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TRANSANNULAR REACTIONS AND INTERACTIONS IN HETEROCYCLIC COMPOUNDS

Reported by Thomas Herrin

June 23, 1965

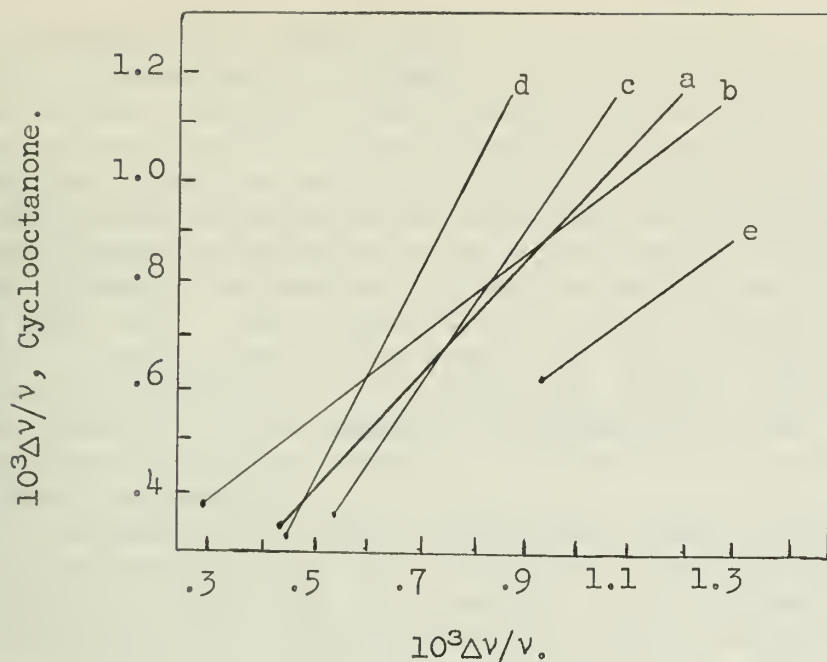
INTRODUCTION

The phenomenon of transannular reaction has been known for over fifty years, one of the earliest examples being reported by Pyman.¹ This property, nearly completely restricted to medium-sized ring compounds, has intrigued several workers. Cope² and Prelog³ have contributed significantly to the knowledge of transannular reactions in carbocyclic rings of eight to ten members while the chemistry of medium-sized rings containing a heteroatom, nitrogen, sulfur, and phosphorous,⁴ has been investigated by Leonard and coworkers.

SULFIDE, SULFOXIDE-CARBONYL INTERACTIONS AND REACTIONS

In the hope of observing transannular effects, Leonard studied medium-sized ring ketosulfides. Compounds of this type were generally prepared by a Dieckmann cyclization of the appropriate diester, subsequent hydrolysis and decarboxylation. Specifically, the starting material for the preparation of 1-thiacyclooctan-5-one (I) was diethyl ~~3,4~~-thia-bis-butyrate (II). When added slowly to a rapidly stirred mixture of potassium *t*-butoxide in a large volume of refluxing xylene under nitrogen, the diester II was converted to the cyclic β -keto-ester. Hydrolysis and decarboxylation of this intermediate gave the desired product.⁵ In nonpolar solvents (cyclohexane and carbon tetrachloride), 1-thiacyclooctan-5-one showed a major absorption band in the infrared spectra at the expected frequency for a cyclic ketone of this size. A shoulder on this peak was attributed to the interaction of the carbonyl group with the sulfur atom. In passing from solvents of moderate polarity (trichloroacetonitrile and acetonitrile) to those of higher hydrogen bonding power (methylene chloride and chloroform), the band at lower frequency corresponding to the interaction increased in intensity and finally predominated.⁶ The frequency shift was greater than that observed in a number of model systems, suggesting that a change in bond order of the carbonyl group occurs. Some doubt has been expressed concerning the reliability of employing the carbonyl band as an index of transannular interactions, since Fermi resonance and/or combination bands may cause splitting of the bands in the 6μ region.⁷ The oxygen analog of I, 1-oxacyclooctan-5-one (III), possesses a single sharp symmetrical carbonyl peak which suffers the same frequency shifts on varying solvent polarity as did cyclooctanone, indicating little or no transannular interaction in either case.⁸ The solvent dependency of transannular effects in interacting and noninteracting systems has been demonstrated effectively through analysis of the infrared data by a method similar to that used by Bellamy and Williams.⁸ When the ratio of the change in frequency to the frequency for cyclooctanone (IV) was plotted against the same ratio for the compounds of interest in a variety of solvents, straight lines were obtained. This is shown in Figure 1. In the absence of gas phase data, the shift in frequency was measured using the carbonyl absorption in cyclohexane as the standard. 5-Methylmercapto-2-pentanone (V), cyclohexanone (VI), and 1-oxacyclooctan-5-one (III) gave straight lines, indicating a normal response in carbonyl absorption to a change in solvent. The values obtained for 1-thiacyclooctan-5-one (I) gave rise to two line segments based upon the frequency values obtained from the noninteracting (higher frequency) bands, and the frequency values from interacting bands (i.e. those which increase in intensity in polar solvents). This illustrates the dependency of the interacting species on solvation.

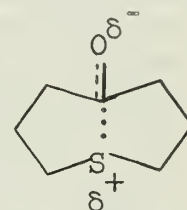
The ultraviolet spectrum of the thioketone I, in contrast to the spectrum of the oxygen analog III ($\lambda_{\text{max}}^{\text{EtOH}}$ 272 μ , ϵ 16.4), was unusual for a saturated cyclic ketone of this size with respect to absorption maximum and intensity. The electronic transition appeared at 226-242 μ (ca. ϵ 2400-2800), with the transition energy being an approximately linear inverse function of the Kosower-Z value.⁹ A bathochromic shift was observed in passing from cyclohexane to solvents of higher polarity as measured by the Z parameter. These facts are consistent with an excited state of higher dipole moment than the ground state. Thus the excited electronic state may



Infrared analysis for: a, 5-methylmercapto-2-pentanone; b, cyclohexanone; c, 1-oxacyclooctan-5-one; d (noninteracting), e (interacting), 1-thiacyclooctan-5-one.

Figure 1

have as a major contributor structure VII. (An $n \rightarrow \pi^*$ excitation would seem to be ruled out by these data since a hypsochromic shift would be expected in changing from cyclohexane to solvents of higher polarity.) Leonard has viewed the excited state as an effective electron transfer from the divalent sulfur atom to the diametrically placed carbonyl group. Ultraviolet spectra similar to those of I have been observed for thioesters (e.g. acetylthiocyclohexane, $C_6H_{11}SCOCH_3$, λ_{max} 231.5 m μ , ϵ 4500¹⁰). Thus in the ground state (as indicated by the infrared spectra) and excited state, transannular interactions are occurring.



VII

Dipole moments for 1-thiacyclooctan-5-one and 1-oxacyclooctan-5-one were calculated⁷ using dipole moments from model compounds and dihedral angles measured from Dreiding models for the crown, twisted boat, and folded conformations. The resultant dipole moments were then a vector sum of the individual dipoles. The results are summarized in Table I. The high dipole moment of 1-thiacyclooctan-5-one (3.81 D) shows that the time-averaged conformation of this ketone, in benzene, has as a major contributor, a folded conformation. It is important to remember that transannular interactions leading to charge separation could raise the resultant dipole moment above the vector sum of the individual moments. This has been observed in the case of the analogous tertiary amino-ketone system.¹¹

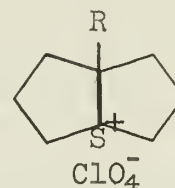
Table I
Dipole Moments

Compound (in benzene)	μ , Debye
Cyclooctanone	2.93
Diethyl ether	1.22
Diethyl sulfide	1.58
Diethyl sulfoxide	3.85
1-Thiacyclooctan-5-one	3.81
1-Oxacyclooctan-5-one	4.09
1-Thiacyclooctan-5-one-1-oxide	3.37

The higher dipole moment for 1-oxacyclooctan-5-one (4.09 D) requires a preponderance of the folded form for the time-averaged conformation for this compound. However, the lack of interaction demonstrates the multiplicity of factors which may influence transannular interactions. The effectiveness of electron transfer is compounded by several factors, besides proximity of functional groups, such as electronegativity, effective orbital radius, and resistance to ring flexion.

A transannular reaction was effected when thiacyclooctan-5-one and 70% perchloric acid were mixed together.⁶ The resulting perchlorate salt, 5-hydroxy-1-thioniabicyclo[3.3.0]octane perchlorate (VIII), possesses hydroxyl absorption, but no carbonyl band was observed in the infrared spectrum (Nujol mull). The

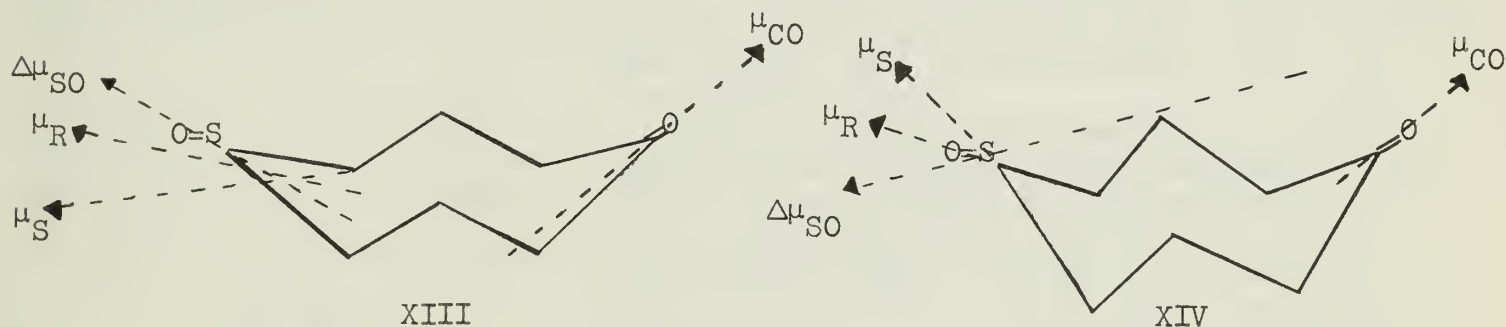
bridgehead substituted methoxy perchlorate IX is formed when the hydroxy perchlorate VIII is dissolved in methanol. In a similar manner VIII in acetic anhydride yielded 5-acetoxy-1-thioniabicyclo[3.3.0]octane perchlorate (X). Further evidence that VIII dissociates into the free ketone I and perchloric acid was obtained from the infrared spectrum. While the Nujol mull spectrum of the perchlorate salt VIII was transparent in the carbonyl absorption region, in deuterium oxide a carbonyl band corresponding to the free ketone was observed at 1667 cm^{-1} . The dissociation was also detected by n.m.r. spectroscopy. The spectra of the salts in deuterium oxide were the same as the ketone except that the position of the signals corresponding to the methylene hydrogens alpha to the thioether group were solvent dependent.



VIII, R=OH
IX, R=OCH₃
X, R=OCOCH₃
XI, R=H

Overberger and Lusi¹³ found that reduction of 1-thiacyclooctan-5-one with lithium aluminum hydride, subsequent treatment with phosphoric anhydride, purification by ion exchange and addition of picric acid gave 1-thioniabicyclo[3.3.0]octane (XI) picrate in 57% yield.

Leonard and Johnson⁷ have extended transannular interactions to the sulfoxide of I. 1-Thiacyclooctan-5-one-1-oxide (XII) was formed in 91% yield when 1-thiacyclooctan-5-one was stirred overnight in an ice bath with a slight excess of aqueous sodium metaperiodate. The electric dipole moment of 1-thiacyclooctan-5-one-1-oxide (measured in benzene) along with the dipole moments of model compounds previously given (Table I) permitted the dihedral angle to be calculated. In determining the dihedral angle of the sulfoxide ketone XII, the resultant dipole moment vector of the sulfoxide group, which does not lie in the C-S-C plane, must be established. Cumper and Walker¹⁴ have reported that the angle between the S=O group and the C-S-C plane in a sulfoxide is 61.5° . This gives a value of $\Delta\mu_{SO}=2.82\text{D}$ for the change in dipole in the S=O direction in going from the sulfide to the sulfoxide. The dipole moment of 3.37D for 1-thiacyclooctan-5-one-1-oxide indicates an angle of 121° between the carbonyl moment vector (μ_{CO}) and the sulfoxide (μ_R), which is 40° out of the C-S-C plane. This corresponds to an angle of 161° or 81° between the C-CO-C plane and the C-S-C plane. Examination of models showed non-bonding hydrogen-interactions become unfavorable when the dihedral angle is 161° (structure XIII).



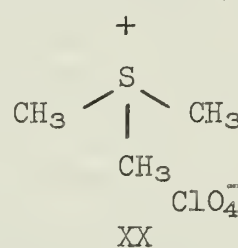
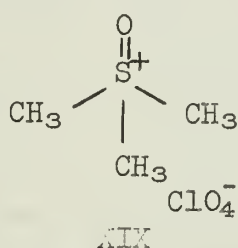
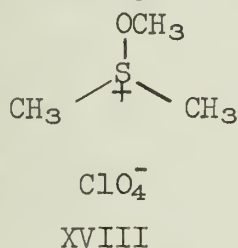
Thus a dihedral angle of 81° (structure XIV) appears to correspond better to the time-averaged conformation of 1-thiacyclooctan-5-one-1-oxide in benzene solution. This dihedral angle leads to a form intermediate between a crown and a folded form.

The infrared spectrum of 1-thiacyclooctan-5-one-1-oxide showed no splitting of the carbonyl or sulfoxide band in a variety of solvents. Both bands were shifted to lower frequency by approximately the same amount as observed in the model compounds (e.g. cyclooctanone and heptamethylenesulfoxide) as the polarity of the solvent increased.

The ultraviolet spectrum of 1-thiacyclooctan-5-one-1-oxide had several abnormal features. A maximum occurred in the 226.5 to 235 mμ region with an extinction coefficient of ca. $\log 2.8$. A hypsochromic shift was observed for this maximum with increasing Z value of the solvent. The parent compound, 1-thiacyclooctan-5-one, as previously stated, exhibited an absorption maximum in the 226 to 242 mμ region with an extinction coefficient of $\log 3.4$; however, a bathochromic shift had been found

for this compound as the polarity of the solvent increased. The change in solvent dependency has been interpreted as reflecting a change in electronic transition. For 1-thiacyclooctan-5-one, the electronic transition was visualized as an electron transfer from the divalent sulfur atom to the carbonyl group. The spectrum of the sulfoxide ketone XII seems to have retained some of the properties of the sulfoxide group for which hypsochromic shifts with increasing polarity of solvent are known.¹² The spectrum of dimethyl sulfoxide or methyl 4-ketopentyl sulfoxide, the open chain model, showed neither an absorption maximum nor a shoulder in this region. Therefore, the electronic transition must be a transannular interaction involving both functional groups.

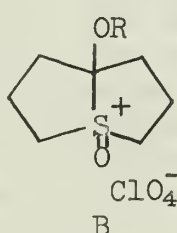
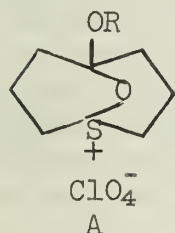
Slow addition of 70% perchloric acid to 1-thiacyclooctan-5-one-1-oxide yielded a perchlorate salt XV. The infrared spectrum of the latter (in acetonitrile) lacked a carbonyl absorption band but possessed a hydroxyl stretching band at 3320 cm^{-1} . The ambident character of the sulfoxide group provides two means of bonding transannularly, one through the sulfoxide oxygen yielding two six-membered rings (type A), and/or through the sulfur atom yielding two five-membered rings (type B). Once again



comparison of XV with model systems proved informative. Dimethyl sulfoxide is capable of forming two alkyl derivatives. The product of kinetic control (O-methylation, XVIII) can be isolated as a product from the reaction of an alkyl arenesulfonate with dimethyl sulfoxide or by treatment of dimethyl sulfoxide with methyl iodide and silver perchlorate. The product of thermodynamic control (S-methylation, XIX) is formed from dimethyl sulfoxide and methyl iodide. The S-alkylated product would be expected to possess a $\rightarrow\text{S}=\text{O}$ absorption band. Kuhn and Trischmann¹⁵ have assigned the 1227 cm^{-1} band in trimethyl-oxosulfonium iodide (Nujol mull) to the $\rightarrow\text{S}=\text{O}$ stretching vibration. With trimethyl-oxosulfonium perchlorate (XX) (in acetonitrile), the absorption is shifted to 1245 cm^{-1} . The perchlorate salt XV and its methoxy as well as the acetoxy derivative, XVI and XVII respectively, have no bands in the infrared spectra in the 1245 cm^{-1} region that are not present in the corresponding sulfonium compounds VIII, IX and X. These

data indicate that the perchlorate salts have structures of type A.

Analysis of the proton magnetic resonance spectra of the sulfoxide ketone perchlorate and its derivatives further support the type A structural assignment for the product of XII and perchloric acid. A list of the chemical shifts for the α -protons for model compounds is given in Table II. The difference in τ -values for the α -protons of trimethylsulfonium perchlorate (XX) and the α -protons of 5-acetoxy-1-



XV, R=H
XVI, R=CH₃
XVII, R=COCH₃

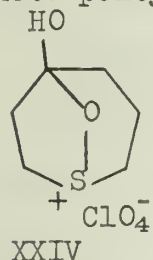
thioniabicyclo[3.3.0]octane perchlorate (X) is 0.74. Approximately the same difference would be anticipated for trimethyloxosulfonium perchlorate (XX) and the bicyclic analog, 5-acetoxy-1-thioniabicyclo[3.3.0]octane-1-oxide perchlorate (XVII B). This approximation leads to a calculated τ -value of 5.38 (6.12-0.74) for the chemical shift of the α -protons in a structure like XVII B. If a value of τ 6.58 is employed for the S-methyl protons of dimethyl-methoxysulfonium perchlorate (XVIII) and a correction of +.15 applied for the transition from a five to a six-membered ring, one obtains 5.99 as an estimate for the τ -value of the α -protons in structure XVII A. With similar treatment of data, Leonard arrived at estimates of 6.20 and 5.58 for the α -protons in XV A and XV B respectively. The observed value for the α -protons of the acetoxy compound (6.25) and the hydroxy compound (6.30) were taken as an indication that structures of type A were correct.

Leonard and Rippie¹⁶ found that transannular reactions similar to those pre-

Proton Magnetic Resonance Data For Model Compounds

Compound, perchlorate	α -protons, τ -values
Trimethylsulfonium	6.97
5-Acetoxy-1-thioniabicyclo[3.3.0]octane	6.23
Trimethyl-oxosulfonium	6.12
Dimethyl-methoxysulfonium	6.58
1-Methyl-1-thioniacyclopentane(XXI)	6.37
1-Methyl-1-thioniacyclohexane(XXII)	6.52

viously given could be effected in the seven-membered analog, 1-thiacycloheptan-5-one-1-oxide (XXIII). In tertiary amino-ketone transannular reactions initiated by strong acid, eight-membered rings were found to be the smallest ring permitting this phenomena.¹⁷ The ambident character of the sulfoxide group permits the formation of a [3.2.0]bicyclic structure and/or the, more favorable ring system, [3.2.1] bicyclic structure. Upon admixture of a saturated solution of XXIII and perchloric acid dissolved in ether, a perchlorate salt is formed. The salt possesses a hydroxy stretching vibration at 3320 cm^{-1} and no absorption at 1245 cm^{-1} previously ascribed to the $\rightarrow\text{S}=\text{O}$ stretching frequency as in trimethyl-oxosulfonium perchlorate. This indicated that the salt is 5-hydroxy-8-oxa-1-thioniabicyclo [3.2.1] octane perchlorate (XXIV). The combination of $\text{S}^+-\text{O}-\text{C}-\text{OH}$ and $\text{S}^+-\text{OH} \text{C}=\text{O}$ type bonding seemed unlikely on the basis of the n.m.r. spectrum and the behavior of methyl 4-keto-pentyl sulfoxide. The original sulfoxide ketone could be recovered by



titrating the salt with base followed by continuous extraction with methylene chloride. This confirms that no acid catalyzed rearrangement had taken place.

The infrared spectrum of XXIII showed no abnormalities, suggesting little or no transannular interactions in the ground state. The ultraviolet spectrum of XXIII in cyclohexane possesses a maximum corresponding to a lower energy carbonyl transition at $287\text{ m}\mu$ and a second absorption at $217\text{ m}\mu$ which is in the region for the absorption of several model sulfoxides. There was no absorption in the $235\text{ m}\mu$ region which was sensitive to solvent changes as observed for 1-thiacyclooctan-5-one-1-oxide.

AMINO-KETONE INTERACTIONS AND REACTIONS

Cyclic tertiary amino groups are known to interact with carbonyl groups located diametrically across the ring.¹⁸ Bell and Archer¹⁹ have found that 3 α -phenyl-3 β -tropanyl phenyl ketone (XXV) possessed an abnormal ultraviolet spectrum in methylene chloride and methanol. The spectrum (see Figure 2) of XXV exhibited decreased absorption and lack of an absorption maximum in the $240\text{--}250$ and $320\text{ m}\mu$ region and showed a significant decrease in intensity in changing solvents from methanol to methylene chloride. The ultraviolet spectrum of the model compound XXVIII was virtually identical in both solvents. The infrared spectrum of XXV in methanol showed no absorption in the 6μ region but in methylene chloride a peak was observed at 6.02μ . Compound XXVIII has a peak at 5.96μ in both solvents.

The possibility of hemiketalization of XXV seems unlikely on the basis of steric hindrance. Furthermore, it would be difficult to explain why interactions occur in XXV and not in XXVI and XXVIII. Since both XXVI and XXVIII showed normal spectral behavior, the 3 α -phenyl and the ethylene bridge are necessary features in causing the abnormal ultraviolet spectrum in XXV. Evidently, the steric repulsion between the 3 α -phenyl and the ethylene bridge forces the molecule into a boat conformation wherein the amine and ketone functions are close enough to interact. The rising absorption in the $230\text{ m}\mu$ region is probably the result of phenyl conjugation with the new chromophore. (Leonard has observed an absorption in the $230\text{ m}\mu$ region in interacting amino-ketones not present in their acyclic analogs.²⁰) These authors suggested the increase in nitrogen-carbonyl interactions in changing from methylene chloride to methanol resulted from better solvation of the charge-separated species in the more polar solvent. Compound XXVII in bromoform showed a hydroxy absorption

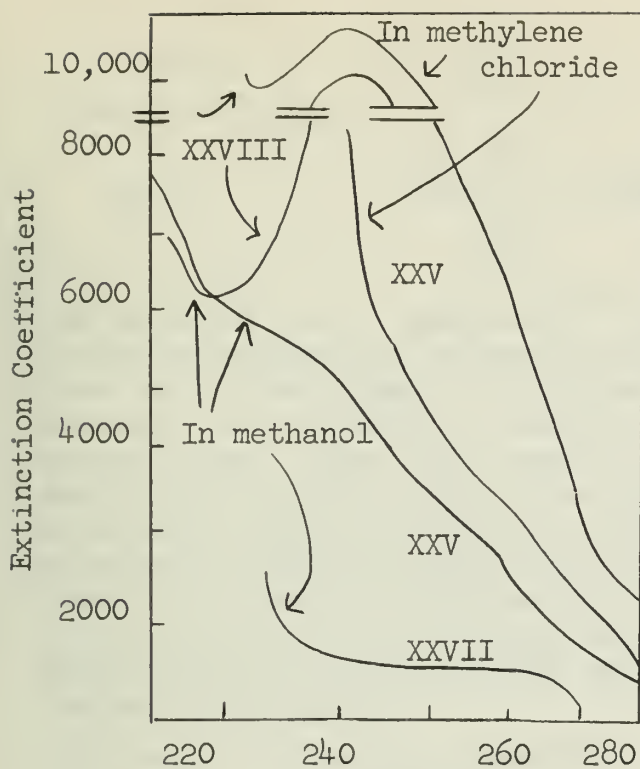
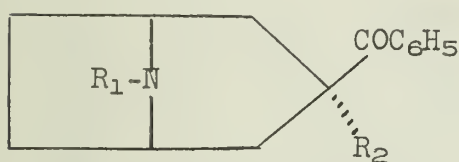


Figure 2 - Ultraviolet spectra of XXV, XXVIII and XXVII in methanol and methylene chloride.

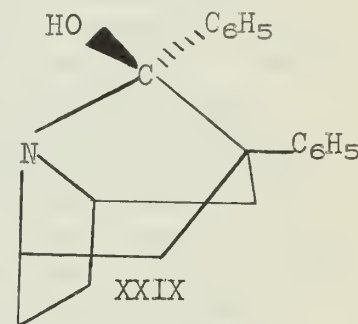
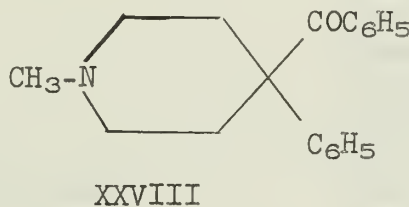
at 2.84μ and no carbonyl band in the infrared spectrum and only weak absorption in the ultraviolet spectrum, suggesting that XXVII exists in solution as the carbinol amine XXIX.

Leonard, Morrow and Rogers¹¹ found 11-methyl-11-azabicyclo[5.3.1]hendecan-4-one (XXX) in a $1.24 \times 10^{-2}M$ carbon tetrachloride solution had a single peak in the 6μ region at 1657 cm^{-1} indicating strong interactions in the ground state. The ultraviolet spectrum was similar to other transannularly interacting amino-ketone systems. Addition of perchloric acid to XXX effected a transannular reaction. The infrared spectrum of the perchlorate salt possessed a strong hydroxyl band (mull) at 3365 cm^{-1} and no maximum in the carbonyl region. With this evidence, structure XXXI seems reasonable. The maximum dipole moment theoretically possible for XXX based on a linear addition of the dipole moments of 1-methylpiperidine (0.80 D) and cyclohexanone (3.07 D) would be 3.87 D. The dipole moments calculated for the possible conformations of XXX fall considerably short of the experimental value (4.87 D). This increase in dipole

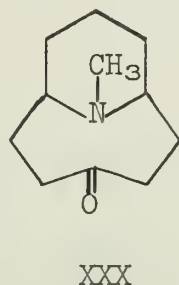
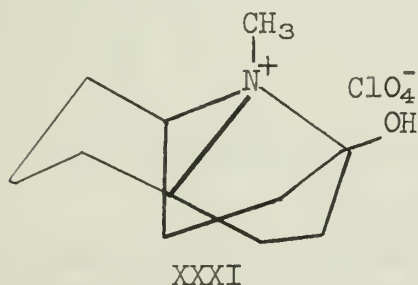
moment (1.00 D) over the highest calculated moment shows there is considerable charge



XXV, $R_1 = \text{CH}_3$; $R_2 = \text{C}_6\text{H}_5$
 XXVI, $R_1 = \text{CH}_3$; $R_2 = \text{H}$
 XXVII, $R_1 = \text{H}$; $R_2 = \text{C}_6\text{H}_5$

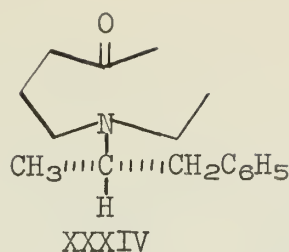
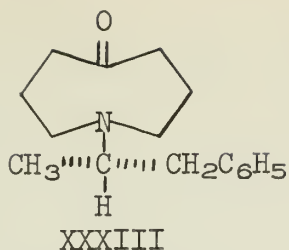
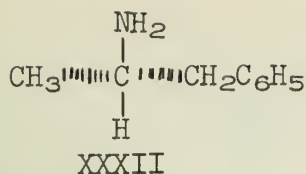


separation caused by transannular interactions. A full charge separation would give rise to a dipole moment of 11-12 D, thus the partial charge separation can be estimated roughly as 11-12%.



Transannular interactions in cyclic amino-ketones might cause abnormal rotatory dispersion curves if a carbon atom alpha to the interacting functional groups were asymmetric. With this in mind, Leonard, Djerassi and coworkers²¹ prepared such a compound and an acyclic model for comparison. The optically active amine chosen was

(+)- α -methylphenethylamine ((+)- α R-methylphenethylamine) (XXXII) whose absolute configuration has been determined.^{22a,b} The conversion of XXXII to (+)-1-(α -methylphenethyl)-1-azacyclooctan-5-one (XXXIII) and (+)-5-(N-ethyl- α -methylphenethylamino)-2-pentanone (XXXIV) was done in such a manner as to leave the stereochemistry of the starting amine unaltered. The rotatory dispersion curve for the open chain amino-ketone XXXIV was a positive plain curve over the wavelength region used (see Figure 3). The shape of the curve was not altered by protonation since XXXIV in 2N hydrochloric acid also gave a positive plain curve. In contrast to XXXIV, XXXIII showed a strong



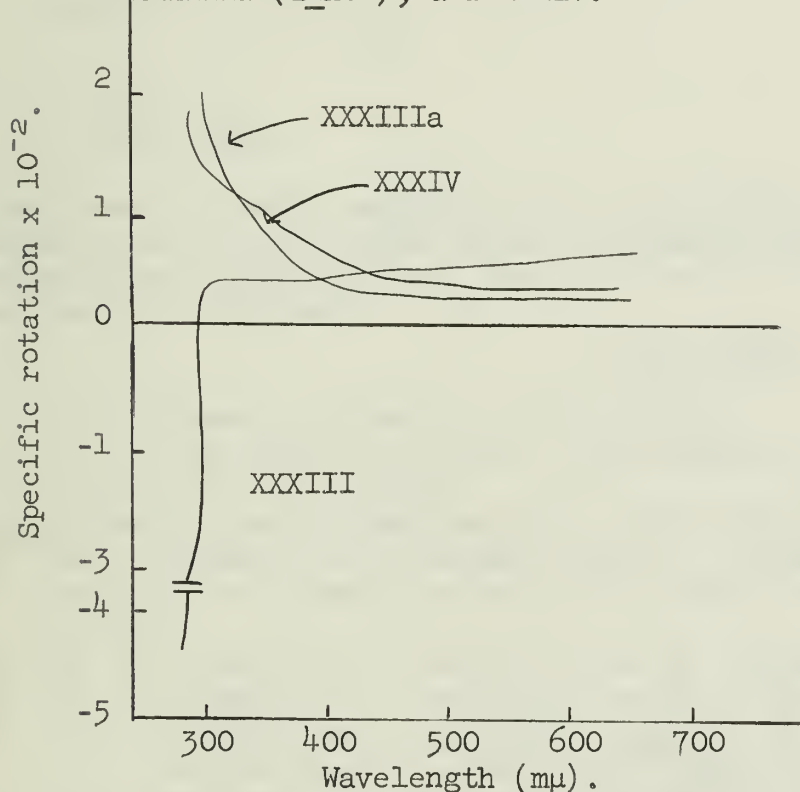
negative Cotton effect superimposed on a positive plain curve. To explain this anomaly, these authors assumed electronic interaction was occurring between the nitrogen atom and

the carbonyl group. Djerassi^{23a,b} has shown that optically active 3-methylcycloheptanone exhibits an abnormal rotatory dispersion curve while 4-methylcycloheptanone does not. Thus asymmetry at the second carbon removed from the carbonyl group is effective in promoting an abnormal dispersion curve while asymmetry at the third carbon is not. This would seem to explain the normal behavior of the acyclic model. When the ultraviolet absorption group was removed by reduction to (+)-1-(α -methylphenethyl)-1-azacyclooctan-5-ol (XXXV), a normal positive curve was obtained. A solution of XXXIII in 2N hydrochloric acid displayed a positive plain curve. The normal curve can be explained by N-protonation preventing transannular interaction or by O-protonation destroying the carbonyl group. The latter explanation was preferred since the hydrochloride of XXXIII in deuterium oxide exhibited little or no carbonyl absorption.

AMINO-AMIDE TRANSANNULAR REACTIONS

Paquette and Wise in studying the transannular reactions of eight and nine-membered

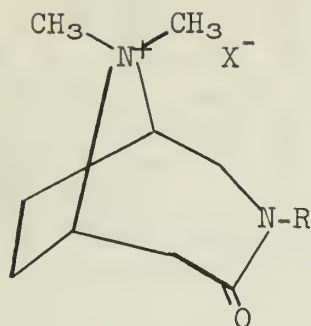
Figure 3 - Optical rotatory dispersion curves for XXXIII (methanol), XXXIIIa (2NHCl), and XXXIV.



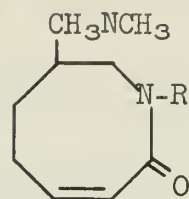
amino-lactams have forcefully demonstrated the strong dependency of transannular reactions on conformational orientation. A Hofmann degradation of 9-methyl-3, 9-diazabicyclo[4.2.1]nonan-4-one methiodide (XXXVI) provided the α , β -unsaturated lactam XL.²⁴ Treatment of XL with ethanolic perchloric acid gave a perchlorate salt in quantitative yield which was shown to be the product of N-protonation, but upon recrystallization was converted to the thermodynamically more stable bridged structure XXXVIII. A similar sequence of reactions was used to extend this concept to the N-methyl analog.²⁵ Thus a Hofmann elimination of the quaternary salt XXXVII gave 1-methyl-7-dimethylamino-5,6,7,8-tetrahydro-2(1H)-azocinone (XLI). Admixture of XLI with ethanolic perchloric acid yielded a crystalline perchlorate salt resulting from N-

protonation. When the N-protonated salt was heated under reflux in ethanol for several hours, no indication of the formation of XXXIX was found. Hofmann elimination of the quaternary salts XLII and XLIII gave XLIV and XLV, respectively. Addition of ethanolic perchloric acid to an ethereal solution of XLIV gave initially a gummy material, which upon heating afforded a crystalline perchlorate salt XLII in high yield. The N-methyl derivative XLV likewise gave rise to a crystalline perchlorate salt; however, it was shown to be the salt resulting from N-protonation.

Paquette and Wise found an explanation for these phenomena by examining Dreiding models of the secondary and tertiary amides. Dreiding models of XL and XLIV show the non-bonding interactions to be minimized when the dimethylamino

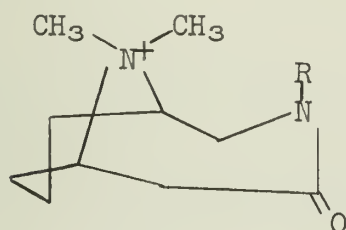


XXXVI, R=H; X=I
 XXXVII, R=CH₃; X=I
 XXXVIII, R=H; X=ClO₄
 XXXIX, R=CH₃; X=ClO₄

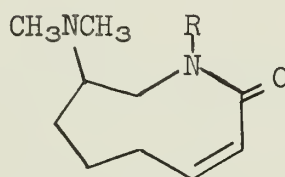


XL, R=H
 XLI, R=CH₃

group is situated within bonding distance to the β -olefinic carbon. The result of introducing the methyl group on the nitrogen atom is to twist the $\text{N}-\text{C}=\text{O}$ bond from



XLII, R=H
 XLIII, R=CH₃



XLIV, R=H
 XLV, R=CH₃

its normally planar configuration to alleviate the steric repulsion between the oxygen atom and the methyl group. Rotation about the $\text{N}-\text{C}=\text{O}$ bond displaces the dimethylamino group further from the olefinic linkage, making a transannular reaction very difficult.

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HETARYNES

Reported by Richard A. Larson

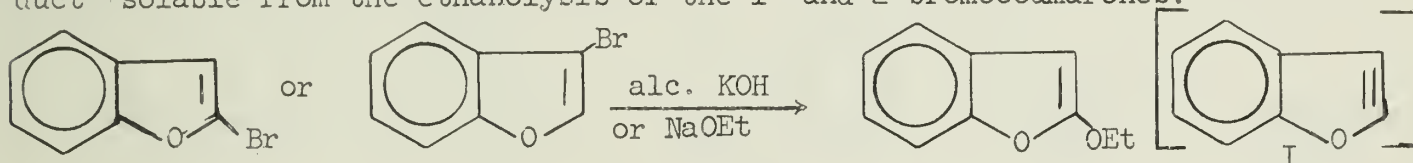
June 25, 1965

INTRODUCTION

Roberts and his coworkers, in 1953, postulated the transient existence of 1,2-dehydrobenzene, or "benzyne", to explain some anomalies of nucleophilic substitution on chlorobenzene which could not be accommodated by the classical addition-elimination mechanism.¹ The benzyne, or elimination-addition, mechanism has since been reviewed quite thoroughly for carbocyclic aromatic compounds.²⁻⁵ However, a growing body of work which has gone almost unnoticed by reviewers is concerned with heterocyclic analogs of benzyne-"hetarynes".

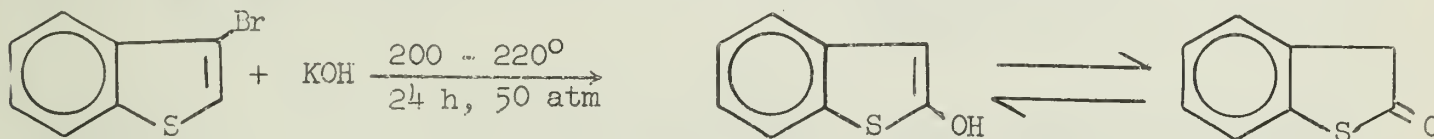
In this seminar the evidence for the existence of hetarynes and some of the chemistry of these intermediates will be reviewed.

The rearrangement of a heterocyclic halide under basic conditions was first reported in 1902, when Stoermer and Kahlert observed that 1-ethoxycoumarone was the only product isolable from the ethanolysis of the 1- and 2-bromocoumarones:⁶



The authors postulated that the hypothetical intermediate I could have been formed by dehydrobromination. This appears to be the first mention of a hetaryne in the literature.

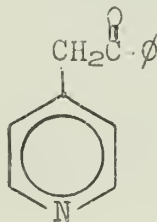
One additional rearrangement of a similar type may be mentioned. The action of ethanolic KOH on 3-bromothiophene has been reported to proceed as indicated.⁷



No 3-keto derivative could be isolated. There was no speculation on the mechanism, but conceivably a hetaryne intermediate may be involved.

PYRIDINES

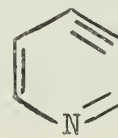
In 1955, Levine and Leake attempted to prepare the then-unknown 3-phenacylpyridine by treating 3-bromopyridine with NaNH₂ and acetophenone in liquid ammonia.⁸ They were unable to isolate any of the desired isomer, but did obtain compound II and the aminopyridine III in yields of 13.5% and 10%, respectively. They proposed that a "pyridyne" intermediate, presumably IV, 3,4-pyridyne, had been formed.



II

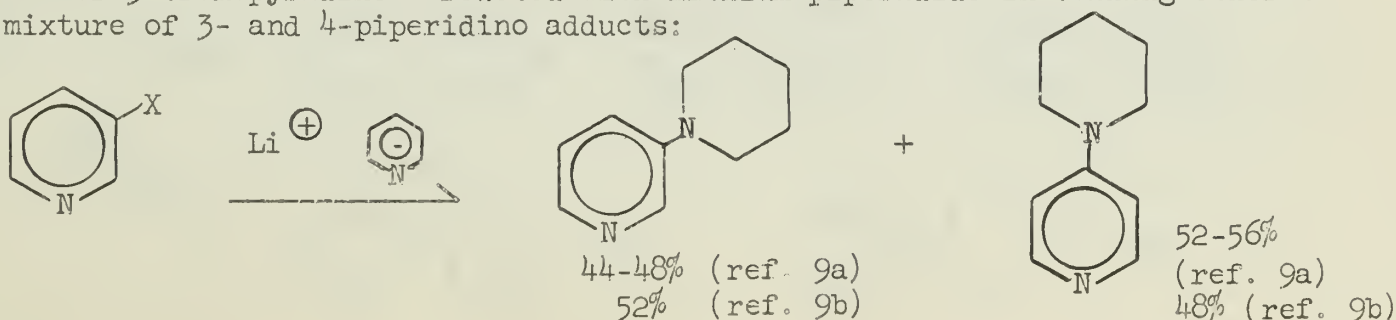


III



IV

Several years later Kauffmann and Huisgen independently reported that 3-chloropyridine^{9a} or 3-bromopyridine^{9b} reacted with lithium piperidide in boiling ether to give a mixture of 3- and 4-piperidino adducts:

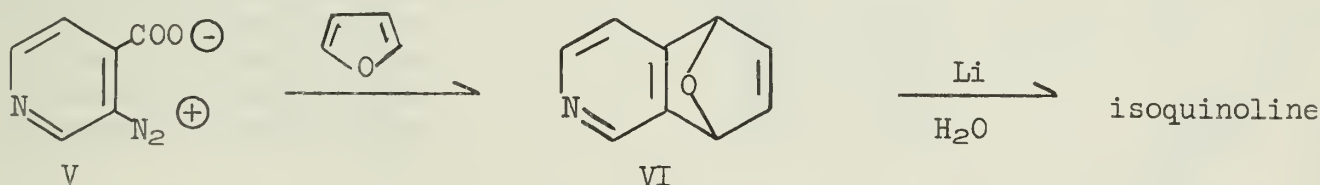


In contrast, 2- or 4-halopyridines^{9,10} or 3-fluoropyridine¹¹ under the same conditions gave nearly quantitative yields of the "normal" (addition-elimination mechanism) isomer.

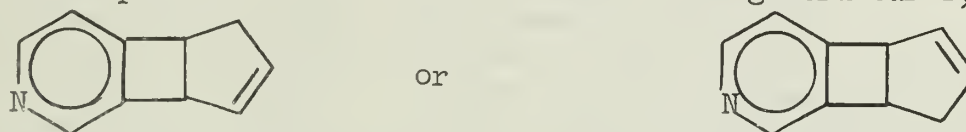
3,4-Pyridyne also adds to dienes in a manner reminiscent of benzyne. It was reported that isoquinoline can be obtained in 14% yield according to the following sequence.^{9a}



Isoquinoline was also isolated in 14% yield when the betaine V was shaken for 7 days at room temperature in furan solution containing lithium amalgam.^{12,13} The intermediate VI may be isolated in the absence of lithium and is converted to isoquinoline under the reaction conditions.



Pyridyne generated from V also adds to cyclopentadiene,¹⁴ yielding a tricyclic adduct which is presumed to have one of the following structures, although no data



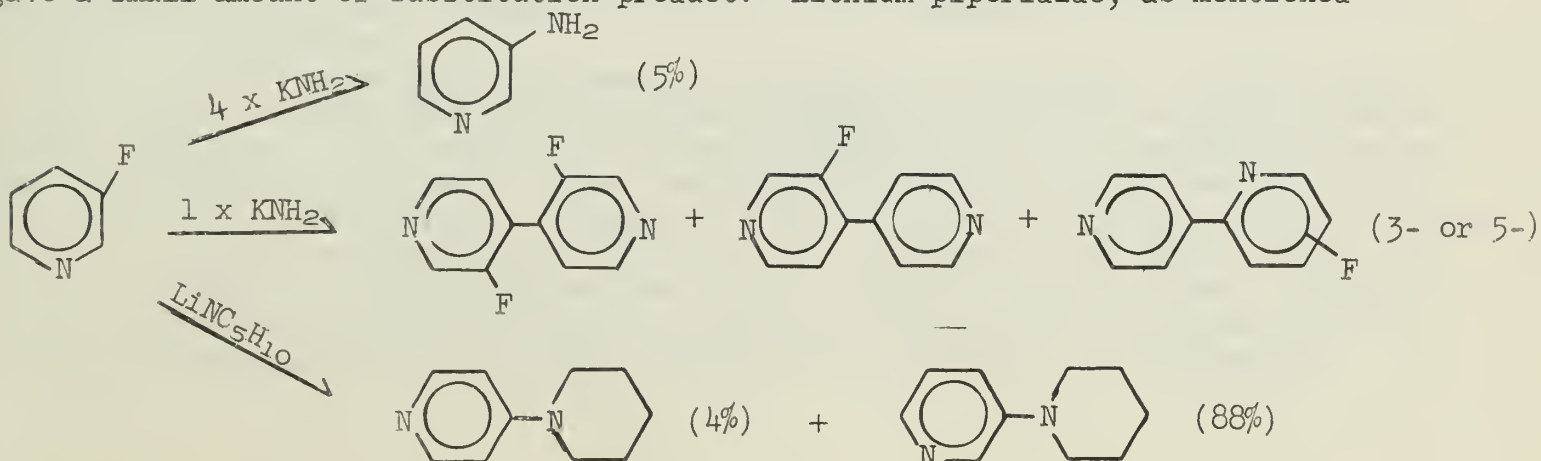
are provided to rule out a 1,4-addition product.

Amination of 3- or 4-halopyridines with KNH_2 in liquid ammonia also leads to products whose formation may be rationalized by invoking a 3,4-pyridyne intermediate.¹⁰



No trace of 2-amino compound could be detected in either case. Interestingly, the 3:4 ratio is the same in the case of either starting material, but it is not 1:1.

The amination of 3-fluoropyridine does not appear to proceed by either the addition-elimination or the hetaryne mechanism. When equimolar amounts of 3-fluoropyridine and KNH_2 were used, only coupling products were isolated.¹⁵ A large excess of KNH_2 gave a small amount of substitution product. Lithium piperidide, as mentioned



previously, appears to react almost exclusively via the addition-elimination route.¹¹

Pieterse and Hertog studied the effects of ethoxy substitution in 3- and 4-bromopyridines.^{10,16,17} It was anticipated that the EtO- group would exert a m-directing effect in such nucleophilic substitution reactions, and thus the relative effects of the two directive influences could be assessed. The results of these studies are summarized in table I.

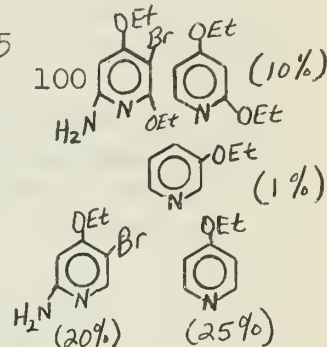
EXP.	Starting compound	Overall yield	Isomer ratio (Amino derivs.)						Other products
			2-	3-	4-	5-	6-		
1	3-ethoxy-4-bromopyridine	90%				100			
2	3-ethoxy-5-bromopyridine	>90%				100			
3	2-ethoxy-4-bromopyridine	85%		2	98				
4	2-ethoxy-3-bromopyridine	90%		3	97				
5	2-ethoxy-5-bromopyridine	95%			65	35			
6	2,4-diethoxy-3-bromopyridine	--							
7	2-ethoxy-6-bromopyridine	90-95%			15	85			
8	2-bromo-3-ethoxypyridine	85%	100						
9	2-bromo-4-ethoxypyridine	95%	100						
10	2-bromo-5-ethoxypyridine	95%	100						
11	4-ethoxy-3-bromopyridine	95%	100						

100
H₂N
N
OEt
Br
OEt
(10%)

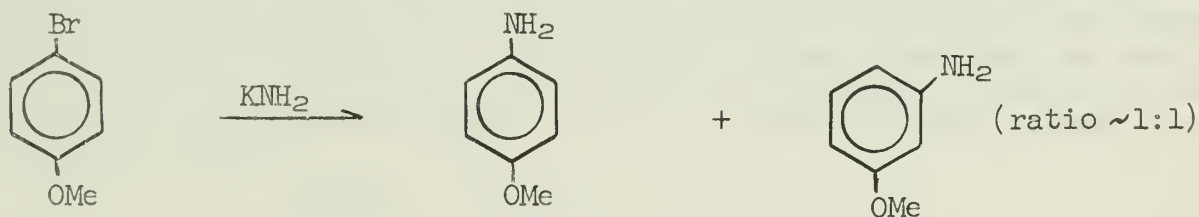
100
H₂N
N
OEt
Br
OEt
(20%)

100
H₂N
N
OEt
Br
OEt
(25%)

100
H₂N
N
OEt
Br
OEt
(1%)



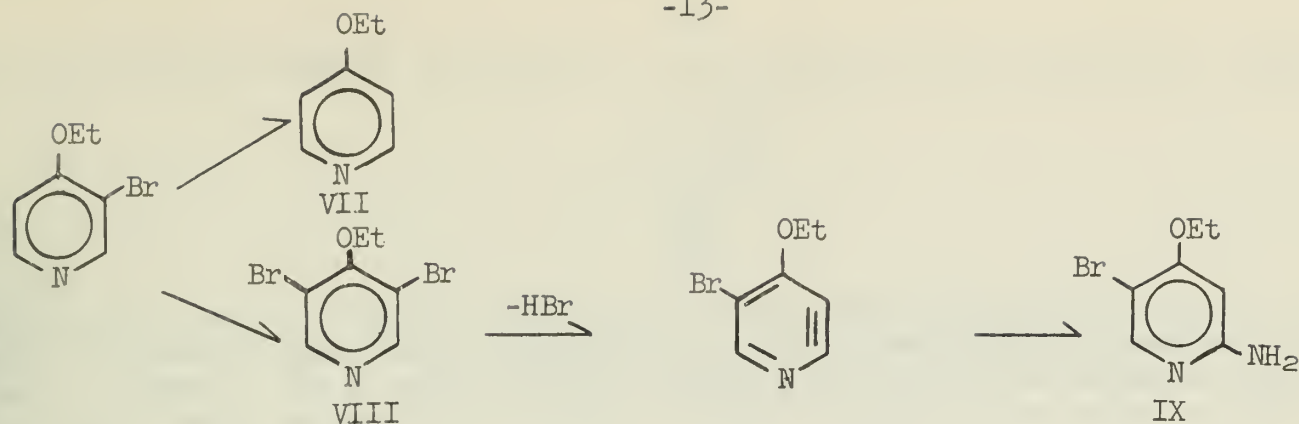
Cases 1 and 2 both support a 3,4-pyridyne intermediate and attest to the m-directing character of the ethoxyl group. The powerful m-directing ability of the EtO- substituent is shown in cases 3 and 4, where despite the great preponderance of the 4-isomer, it seems reasonable to assume that a 3,4-pyridyne intermediate is produced. Notably, in case 5 the ethoxy substituent appears to have no effect: the 1:2 ratio of meta:para (to the nitrogen) is the same as for the unsubstituted bromopyridines. An analogous reaction exists in the benzyne series:¹⁸



The o- and m-bromoethoxybenzenes, in contrast to the above result, give only one compound, the m-aminomethoxybenzene.

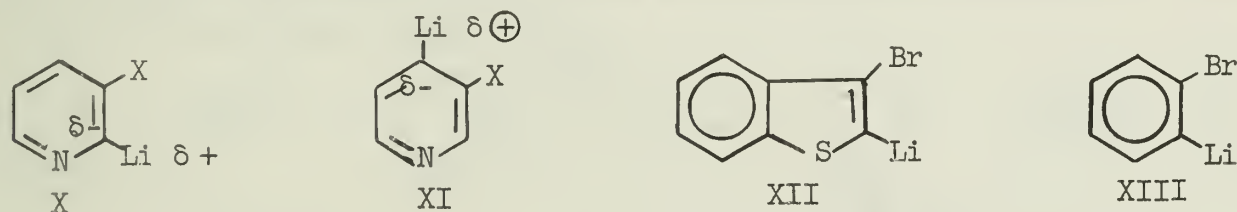
2,3-Pyridyne intermediates do not appear to be formed in the amination of the four possible 2-bromoethoxypyridines (experiment 7-10). The 3-, 4-, and 5-ethoxy-2-bromopyridines give high yields of the 2-amino isomers. This is best explained by the addition-elimination mechanism. 2-Ethoxy-6-bromopyridine (exp. 7) also reacts largely by addition-elimination. In addition, however, a low yield of 2-ethoxy-4-aminopyridine, a rearrangement product in which the entering substituent has taken the position meta to the halogen, is obtained. No explanation is advanced for this remarkable rearrangement.

The results of experiment 11 appear to implicate a 2,3-pyridyne. Here blockage of the 4-position precludes formation of a 3,4-pyridyne, and the rearranged 2-amino isomer, obtained in 55% overall yield, perhaps arises by the 2,3-pyridyne mechanism. The by-products in experiment 11 also may be rationalized by the following scheme, which involves a 2,3-pyridyne; VII and VIII can be isolated from the reaction mixture if the reaction is stopped after one minute. VII was shown to be stable under the reaction conditions, whereas IX and the related compound 2-amino-3-bromo-4-ethoxypyridine do react, by debromination, but very slowly. Thus it is unlikely that any of the reaction products are formed by substitution-debromination mechanisms.



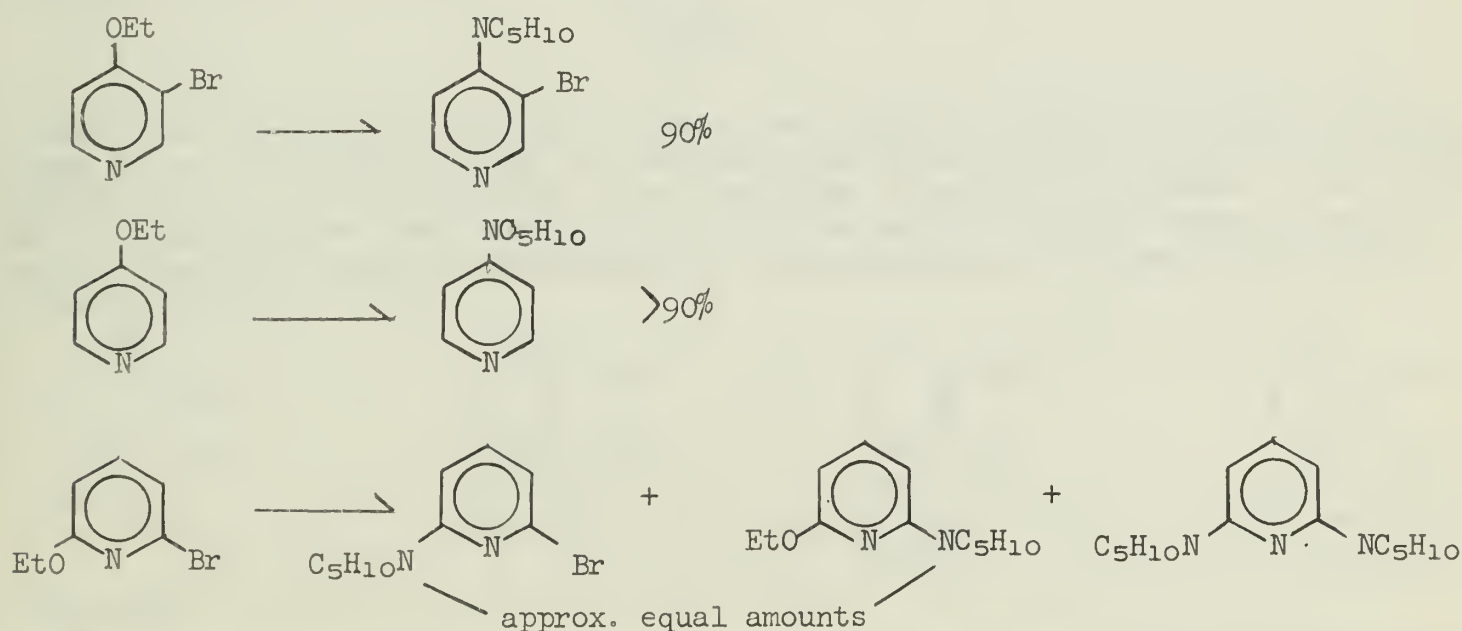
The formation of quinoline when 2-chloro-3-bromopyridine is allowed to react with lithium amalgam in furan solution provides additional evidence for the existence of 2,3-pyridyne.¹⁹ Presumably a 1,4-epoxide intermediate is produced as in the analogous reaction leading to isoquinoline.^{9a} The yield, however, is only 1.5%.²⁰

Kauffmann and Boettcher do not observe products characteristic of 2,3-pyridyne in the reactions of 2- or 3-halopyridines with lithium piperidide in boiling ether.^{9a,11} These authors suggest that in the case of 3-halopyridines, intermediates X and XI might be formed. Possibly only XI would go on to lose LiX, since in X the partial



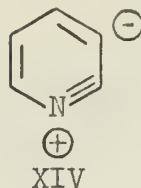
negative charge on C₂ would be stabilized by the nonbonding electron pair on the ring nitrogen. Protonation of X by the solvent piperidine would then lead back to starting material. In support of this idea, it is noteworthy that compound XII is stable at room temperature²¹ whereas the carbocyclic species XIII decomposes even at -100°. ²²

The non-formation of 2,3-pyridyne intermediates in reactions employing lithium piperidide was further documented by a report that lithium piperidide, in reactions with bromoethoxypyridines which could give rise to 2,3-pyridynes, prefers an addition-elimination reaction of an unusual type in which the ethoxyl group is lost in preference to the bromine atom.²³



Martens and Hertog attempted to provide less equivocal evidence for 2,3-pyridyne by using pyridine-N-oxide and ethoxyl derivatives thereof.²⁰ They reasoned that the exclusive formation of 2-aminopyridines from 2-halopyridines might be a result of the tendency for preferential formation of (or large resonance contribution by) intermediates like XIV, which could only yield isolable products at the 2-position.

Accordingly they attempted the amination of 2-chloropyridine-N-oxide and obtained,

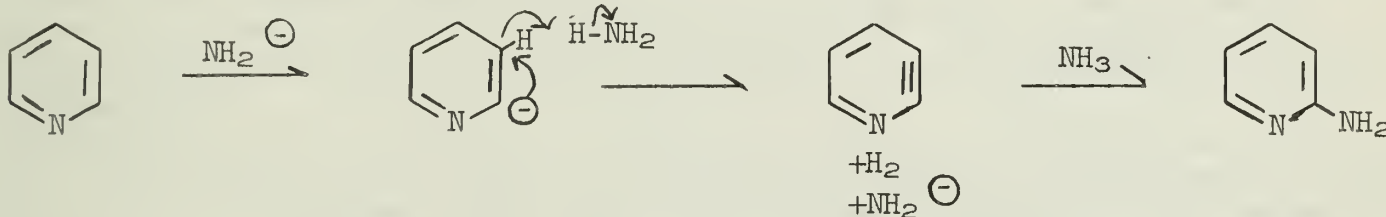


among other products, a mixture of 2- and 3-aminopyridine-N-oxides in unspecified ratio. Presumably the 3-amino product could have arisen through a hetaryne intermediate. However, the 3- and 4- chloro isomers did not give the expected mixture of the 3- and 4-amino compounds, but only the normal addition-elimination product in both cases.

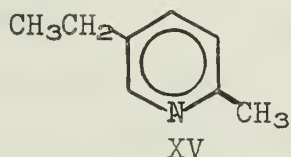
Piperidine also adds to 3-chloropyridine-N-oxide to give 3-piperidino-pyridine-N-oxide, in 16% yield, but in addition about 1% of the starting material is converted to the 4-isomer, which suggests the intermediacy of 3,4-pyridyne-N-oxide.¹⁴

Amination of either the 2- or 3-bromo,4-ethoxypyridine-N-oxides gives only the 3-amino adduct.²⁰ A hetaryne intermediate is postulated in this case also, with the assumption that the m-directing ability of the N-oxide grouping exceeds that of the ethoxyl substituent.

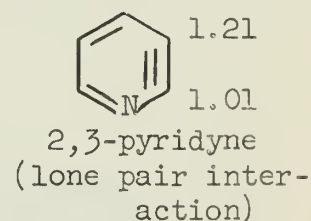
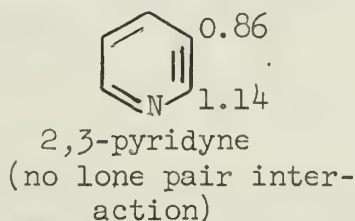
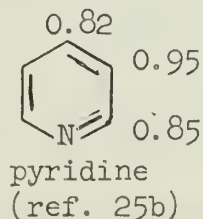
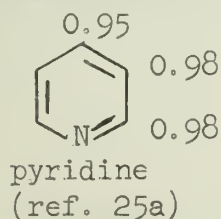
2,3-Pyridyne itself has been proposed as a possible intermediate in the amination of pyridine (Chichibabin reaction):²⁴



The preferential formation of the 6-amino compound when the 2-position is blocked, and the 4-amino compound in cases like XV, where presumably hetaryne formation could not occur, is cited as evidence for the proposal. The amination of 3-hydroxypyridine, which should have given 2-aminopyridine with loss of -OH if the pyridyne mechanism were correct, leads to the production of 2,6-diaminopyridine.



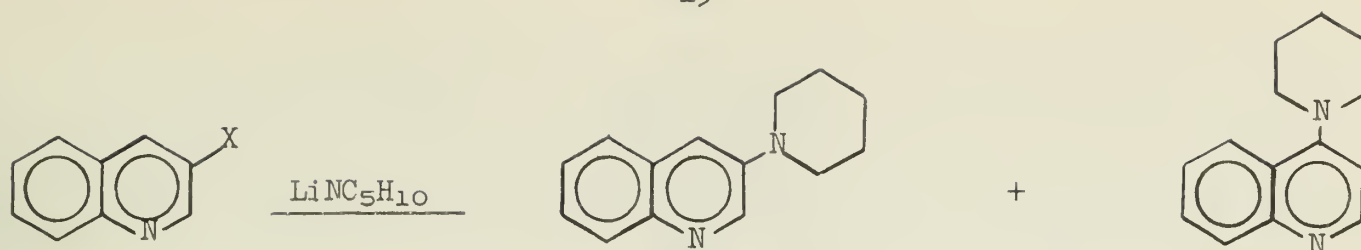
Molecular orbital calculations for pyridine²⁵ indicate that the 4-position has the lowest pi electron density, and thus should be the most favorable site for nucleophilic substitution. As mentioned above, the 2-position is generally preferred. Calculations for 2,3-pyridyne show that the 2-position in this species has the lowest electron density, provided lone pair interaction by the nonbonding electrons of the nitrogen is included.²⁶



QUINOLYNES

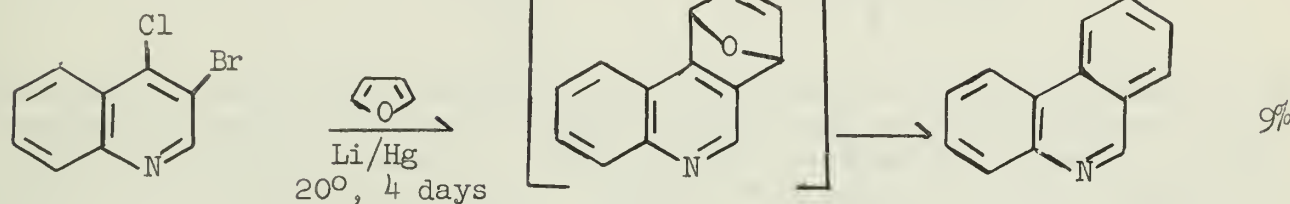
Kauffmann and coworkers demonstrated the existence of 3,4-quinolyne by the following reactions.^{12,27}

a)



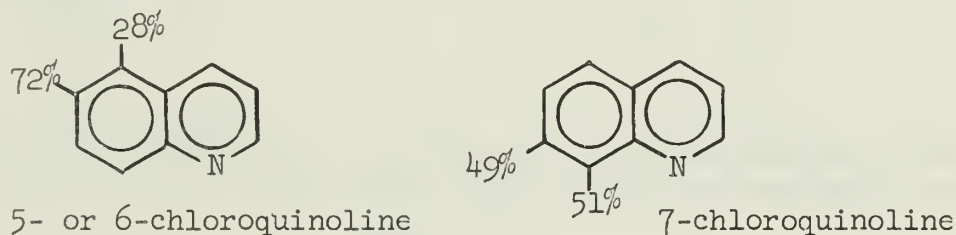
X	Overall yield %	Isomer ratio	
		3-isomer	4-isomer
F	75	100	--
Cl	45	48	52
Br	61	50	50
I	58	49	51

b)



It was later reported that 2-chloro-3-bromoquinoline gave a "small quantity" of acridine when treated with lithium amalgam in furan.²⁸ The 2,3-dichloro analog, in contrast, gave no detectable acridine. Thus there is reason to doubt the existence of 2,3-quinolyne.

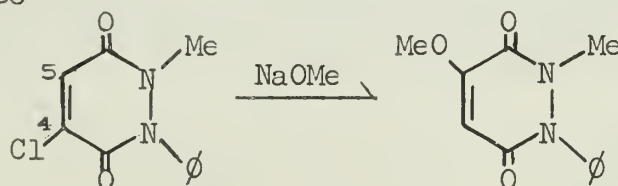
Monobromo- or -chloroquinolines in which the halogen is located in the carbocyclic ring at positions 5, 6, or 7 also give substitution products characteristic of elimination-addition mechanisms when treated with lithium piperidide.²⁹ The isomer distributions are as indicated below. 8-Bromo- or -chloroquinoline gives only the normal addition-elimination product.



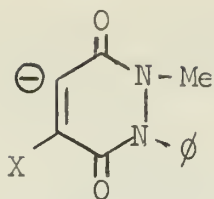
3-Bromoquinoline-N-oxide also appears to form a 3,4-dehydro derivative, as it gives approximately equal quantities of 3- and 4-piperidinoquinoline-N-oxide when heated under reflux with piperidine for several days.¹⁴ The 4-chloro isomer appears to react wholly by the addition-elimination mechanism.

OTHER HETARYNES

Druey, in 1958, reported the following rearrangement of 1-methyl-2-phenyl-4-chloropyridazine-3,6-dione.³⁰

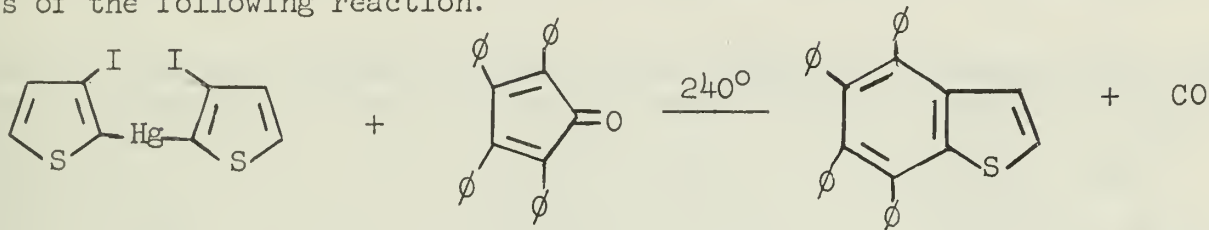


Kauffmann and Risberg reinvestigated the reaction using various nucleophiles.³¹ Piperidine gave the 4- and 5-isomers in the ratio 1:25. If aniline or methanol were added to the piperidine, 5-anilino- and 5-methoxy- derivatives could be obtained as well. If benzene, rather than piperidine, was used as the solvent for the reaction, the 4:5 ratio changed from 1:25 to 1:5.2.³² When ethanol was used as solvent, the ratio was reversed, and became 3.4:1. The corresponding bromo compound in ethanol gave nearly a 1:1 ratio. To explain this reversal, the authors suggested that the formation of carbanion XVI (or synchronous elimination of HX to form the hetaryne) should be slowed in solvents such as ethanol, a better proton donor than piperidine.

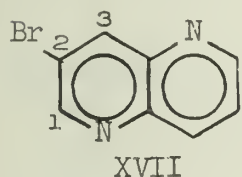


XVI

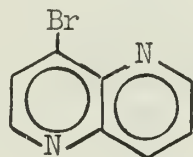
Wittig and Wahl postulated a 2,3-dehydrothiophene intermediate to explain the results of the following reaction.³³



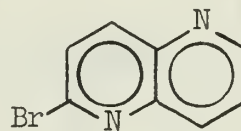
Czuba observed evidence for naphthyridyne intermediates in the amination of the three isomeric bromonaphthyridines.³⁴ The relative constancy of the isomer ratios in the reactions involving compounds XVII and XVIII presumably indicates a large contribution by the hetaryne mechanism. Compound XIX appears to react almost exclu-



XVII



XVIII

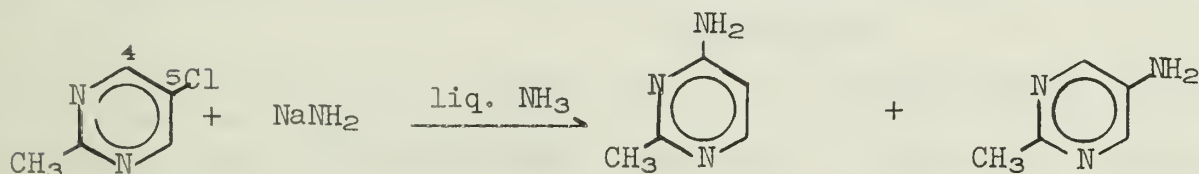


XIX

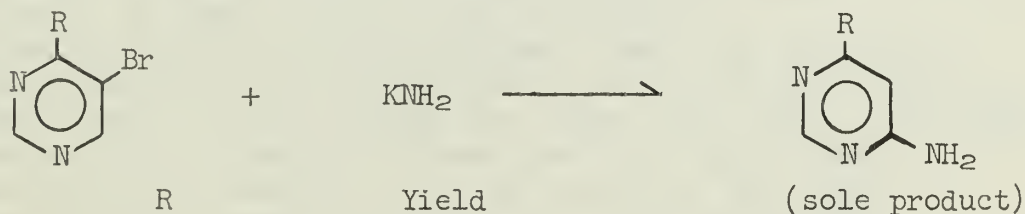
Compound	Yield of aminonaphthyridines (1%)		
	1-	2-	3-
XVII	-	82	13
XXVIII	-	70	20
XIX	77	-	<1

sively by addition-elimination.

Schwan and Tieckelmann postulated a 4,5-pyrimidyne intermediate to explain the amination result shown below.³⁵ The total yield of the two compounds was only about

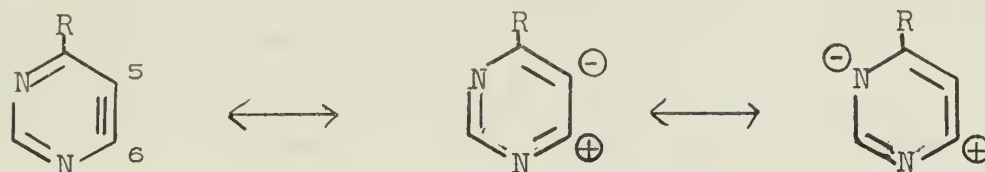


5%, and therefore the isomer ratio was not determined. Kauffmann *et al.* also reported that 5-chloropyrimidine, unlike the 4-isomer, gives a mixture of 4- and 5- piperidino compounds when heated with piperidine.²⁹ 5,6-Pyrimidyne intermediates were proposed by van der Plas and Geurtsen to explain the facile rearrangements of 5-bromopyrimidines substituted in the 4-position to the 6-amino compounds when treated with KNH_2 .^{36,37}

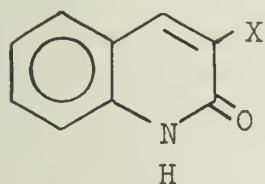


R	Yield
-C ₆ H ₅	15%
-OCH ₃	70%
-OH	75%
-NH ₂	16%
-CH ₃	95%
-t-Bu	13%

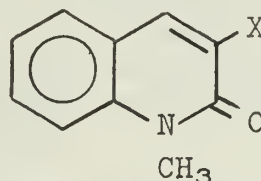
Only when R = -t-Bu was any 5-amino compound isolated, and then in only 1% overall yield. The preference for the 6-position is explained by these authors in terms of resonance contributions of the type indicated.



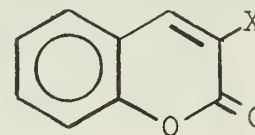
Finally, hetaryne intermediates have been claimed for 3-haloquinolone and 3-halo-coumarin derivatives in their nucleophilic substitution reactions with piperidine.^{29,32}



XX



XXI



XXII

Halogenide	X	Yield piperidino compounds	3-isomer %	4-isomer
XX	-Cl	96%	54	46
XX	-Br	90%	52	48
XXI	-Cl	90%	55	45
XXI	-Br	98%	57	43
XXII*	-Cl	52%	39	61
XXII*	-Br	79%	30	70

* benzene as solvent, others piperidine

Notably, halogenide XXII showed a reversal of the 3:4 ratio (to 60:40 when the chloro compound was used, 72:28 for the bromo analog) when ethanol was used as solvent, as had the pyridazine derivative mentioned earlier.

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USE OF THE TRIMETHYLSILYL BLOCKING GROUP

Reported by Marvin Coon

July 2, 1965

INTRODUCTION

Blocking groups are often used when it is desirable to protect a sensitive site in a molecule either during the course of a reaction or during processes which might result in changing or destroying the functional group involved. For example, acyl derivatives are used for the protection of alcoholic and phenolic groups during oxidation of some other group in the molecule, after which the acyl group is removed by saponification. Acetates have lower boiling points than the hydrogen-bonded hydroxy compounds and they are much less strongly adsorbed on a chromatographic column of alumina. Hence, an alcoholic or phenolic reaction product is often converted to the acetate for better purification by distillation or chromatography. An acetate or benzoate may also offer advantages in crystallization.¹

One of the more recent methods of blocking alcohols, phenols, sulfides, acids and amines is the trimethylsilyl group, $(\text{CH}_3)_3\text{Si}-$, abbreviated as TMS.

The advantages of the TMS group in separation procedures were discussed by R. W. Martin² in 1952. He cites the ease of preparation of TMS derivatives, their excellent thermal stability, resistance to air oxidation, low viscosity, and ease of hydrolysis under neutral conditions as being ideal for the purification or separation of hydroxy compounds sensitive to heat, acid, alkali or air oxidation.

Other workers have found the TMS group useful for blocking thiol, acid and amine groups.³

One of the most outstanding features of the TMS group is its remarkable thermal stability as evidenced by the penta TMS derivative of D-glucose which can be distilled at 760mm at 310° without decomposition,⁶ or the octa TMS derivative of sucrose which can be distilled at 190-200° at 0.05mm without decomposition.⁵

The subject will be considered under the four following categories: 1) preparation of TMS derivatives; 2) use in VPC; 3) use in separation and other procedures; 4) synthetic value.

PREPARATION OF TMS DERIVATIVES

Three general methods are used for preparation of TMS derivatives of alcohols, phenols, acids, amines and mercaptans. The first involves treatment with hexamethyldisilazane, TMS_2NH , from which the TMS derivative and ammonia are formed. The second method requires that the material be treated with trimethylchlorosilane, TMS-Cl , and an acid scavenger, usually ammonia or pyridine. The third and most infrequently used method is an ester exchange with trimethylethoxysilane, TMS-OEt , ethanol being formed as a by-product.

A fourth method, recently introduced by Birkofer⁷ for use with sugars involves treatment of the sugar with N-trimethylsilylacetamide, $\text{CH}_3\text{CONHTMS}$. Acetamide is formed as a by-product.

Generally speaking, most of the above reactions give very high yields of the derivatives with the ester exchange ranking lowest (about 50-70%) and the disilazane method ranking highest (80% or better).

Table I lists specific methods of preparing derivatives with the various functional groups indicated along with literature references.

Table I
Specific methods of preparing TMS derivatives.

functional group	silylating agent	by-product	ref.
ROH or ArOH	TMS-Cl , pyridine	pyridine.HCl	2,8
	TMS_2NH	ammonia	8
	TMSOEt	ethanol	8
sugar-OH	$\text{CH}_3\text{CONHTMS}$	NH_4Cl	7
	TMS-Cl , TMS_2NH	NH_4Cl	10
RCOOH	TMS-Cl , pyridine	pyridine.HCl	6
RSH	TMS-Cl , NH_3	NH_4Cl	9
	TMS_2NH	ammonia	9
RNH_2	TMS-Cl , NH_3	NH_4Cl	9

It should be noted that in nearly every reference cited herein, the authors report that the TMS group is quantitatively removed during hydrolysis with water, alcohols or acidic or basic catalysts. With such a spectrum of cleaving agents, one can choose either neutral, acidic or basic conditions for cleavage of the TMS group, depending upon the particular requirements and sensitivity of the molecule in question. Under neutral conditions, the parent compound, trimethylsilanol, (TMS-OH) and hexamethyldisiloxane (TMS-O-TMS) are obtained (or RO-TMS if ROH is used).

USE OF TMS DERIVATIVES IN VPC

Before the use of TMS derivatives, polyhydroxy compounds and sugars were converted to either acetates or methyl ethers before subjection to VPC analysis.³ The main difficulty with these derivatives is that they are not easily prepared quantitatively and often they are difficult to hydrolyze without rearrangement or decomposition. Allen¹¹ and coworkers discuss the use of BCl_3 as a cleaving agent for these derivatives and difficulties concerned with them.

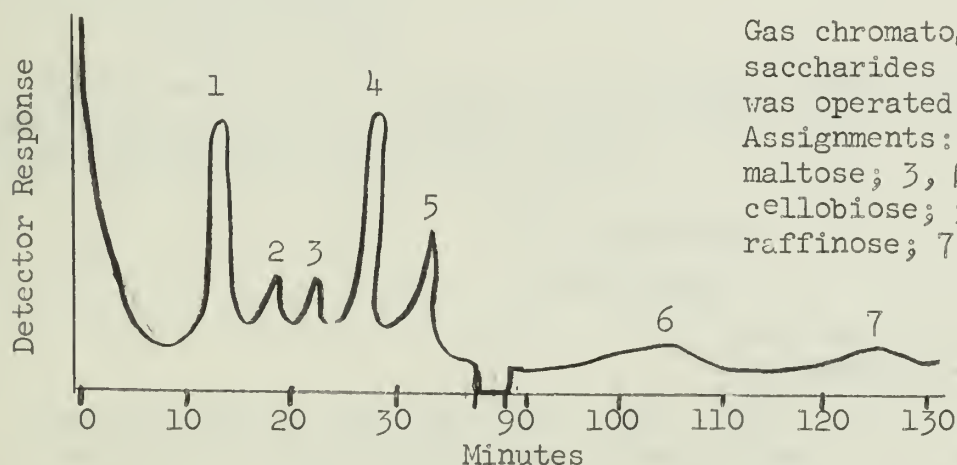
Henglein⁴ and coworkers, as early as 1956 prepared TMS derivatives of glucose and pectin and later of other sugars, diacids and polymers.^{12,13} More recently, other workers have prepared TMS derivatives of sugars.^{10,14}

Chang and Hass⁵ reported the preparation of the octatrimethylsilyl derivative of sucrose in 1958 and because of its thermal stability and volatility suggested that it might be useful in VPC identification. In the same year, Langer¹⁵ and associates, prepared TMS derivatives of phenols occurring in coal tar and used VPC analysis to separate *o*-m- and *p*-cresols.

Hedgley and Overend¹⁴ for the first time applied in 1960 to the analysis of TMS derivatives of sugars. They were able to remove selectively the TMS group in the presence of isopropylidene, benzylidene and glycosidic groups.

Ferrier¹⁶ compared VPC analysis of acetylated, methylated and trimethylsilylated sugar derivatives in 1962. He found that the difference in retention time for TMS substituted anomers was greater than that for methyl substituted anomers.

The most comprehensive study of the VPC of sugars and related substances was done by Sweeley and others,¹⁰ in 1963. The authors describe the chromatographic separation of about 100 carbohydrates and derivatives ranging from C_3 , glyceraldehyde, to C_{24} , stachyose. Methods were worked out for the rapid preparation of TMS derivatives on a micro scale. Suitable column packings were developed and temperatures for best separations described. The method was applied to the analysis of equilibrium mixtures of anomers and found to compare favorably with older methods. Figure 1 is a reproduction from Sweeley's paper of the chromatographic separation of representative di- and trisaccharides.



Gas chromatography of di- and trisaccharides on SE-52. The column was operated isothermally at 210° . Assignments: 1, sucrose; 2, α -maltose; 3, β -maltose; 4, β -cellobiose; 5, gentiobiose; 6, raffinose; 7, melezitose.

Figure 1

More recently Sweeley and coworkers,¹⁷ reported the use of TMS derivatives in the VPC analysis of phosphorylated sugars.

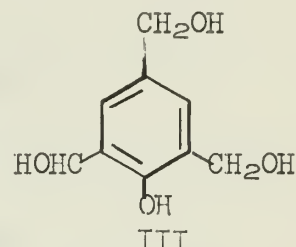
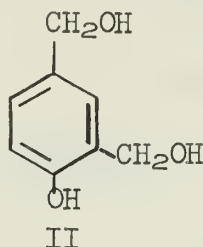
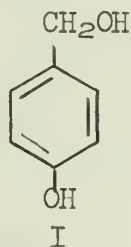
TMS derivatives have also found considerable use in the analysis of hydroxylated steroids. Horning, and others,¹⁸ obtained good results for the analysis of estrogens via their TMS derivatives. They were also able to collect the TMS derivative of

chloestanol from the column unchanged. In another study¹⁹ they compared TMS and trifluoroacetyl derivatives of urinary steroids and found that the TMS derivatives are easier to prepare and give better VPC separation.

Makita and Wells^{20,21} have applied TMS derivatives to the VPC analysis of neutral fecal steroids and bile acids.

USE OF TMS DERIVATIVES IN SEPARATION AND OTHER PROCEDURES

The low viscososity, volatility and thermal stability of TMS derivatives was utilized in the separation by distillation of the products obtained from the treatment of phenol with formaldehyde under basic conditions.² The crude mixture of products (1,11,111), was treated with TMS-Cl and pyridine, then distilled to provide separation. The free phenol-alcohols were obtained pure by cleavage of the TMS groups in a boiling water-alcohol mixture.



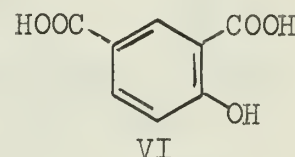
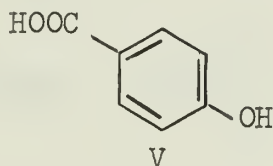
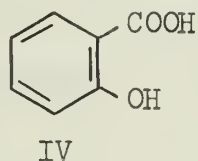
b.p. of
TMS deriv.

90-140°/15mm

115-125°/0.05mm

135-145°/0.05mm

In a similiar manner, Burkhard⁶ used TMS derivatives to achieve the separation of the reaction mixture resulting from carbonation of phenol. From previous experience it was observed that the acids, IV, V, VI, would decarboxylate if heated to high temperatures. However, trimethylsilation followed by distillation and cleavage was found to give the desired products without decomposition and without the less satisfactory crystallization procedures formerly used.



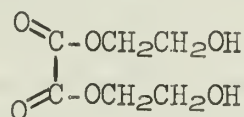
b.p. TMS
deriv.

62°/0.95mm
(77.5°/1.1mm
only phenolic
group blocked)

82°/0.85mm

148-50°/1.0mm

Sprung and Nelson²² applied distillation of TMS derivatives to the purification of ethylene glycol esters of dicarboxylic acids, VII. The same method was employed for the purification of various polyols.



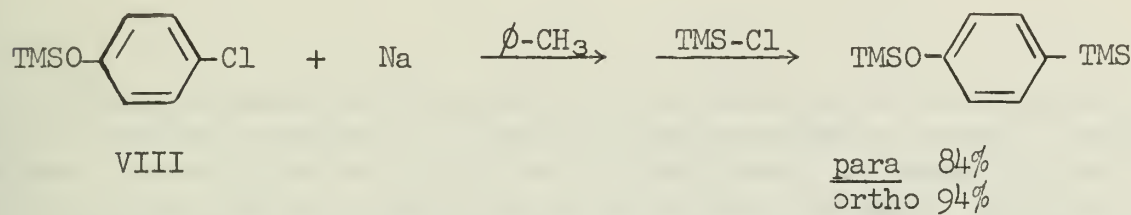
VII (also maleate, phthalate and
terephthalate esters)

TMS derivatives also have been found useful in mass spectroscopy. The ordinary mass spectrum of a C₁₀ alcohol from a conventional room temperature mass spectrometer is not usable, but the spectrum of its TMS derivative is usable. Langer,²³ and coworkers, found that mass spectra of alcohols could be obtained in the presence of hydrocarbons without interference. He has also worked out the fragmentation patterns of the TMS group.

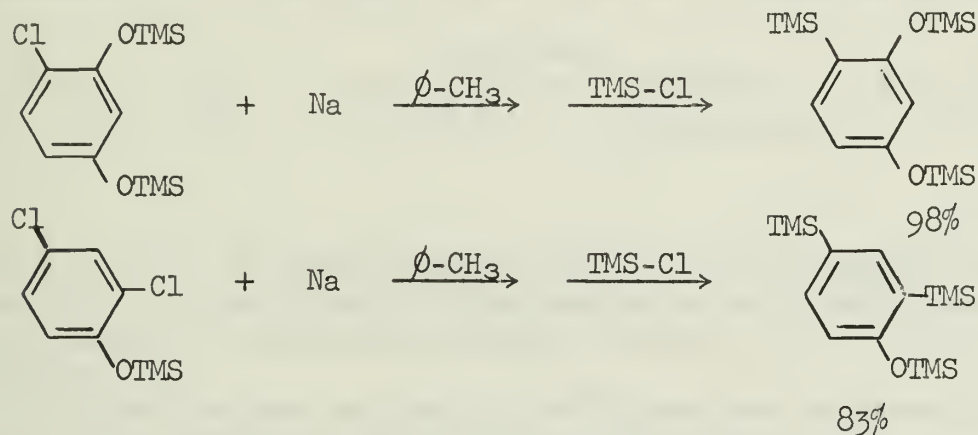
USE OF THE TMS GROUP IN SYNTHESIS

Speier⁸ found the TMS group an ideal way to block halogen containing alcohols

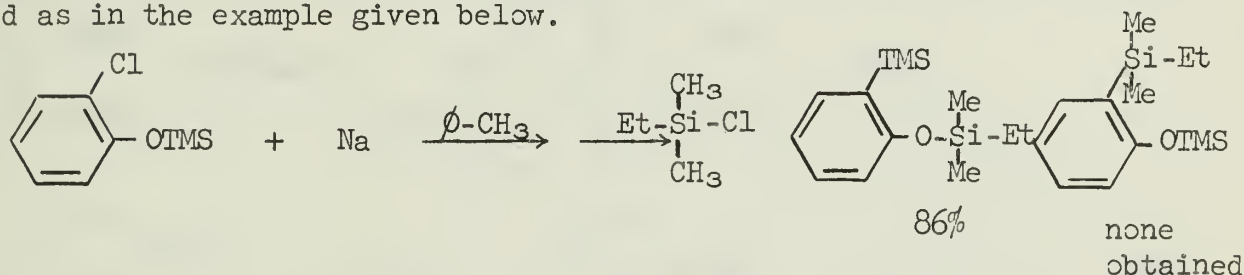
and phenols when it was desirable to prepare organometallic reagents of these compounds. He prepared sodium and potassium reagents of VIII and allowed them to react them with TMS-Cl. Lithium or Magnesium did not form an organometallic reagent.



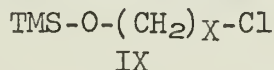
Other examples are cited below:



Speier observed that with aryl-sodium reagents rearrangements sometimes occurred as in the example given below.

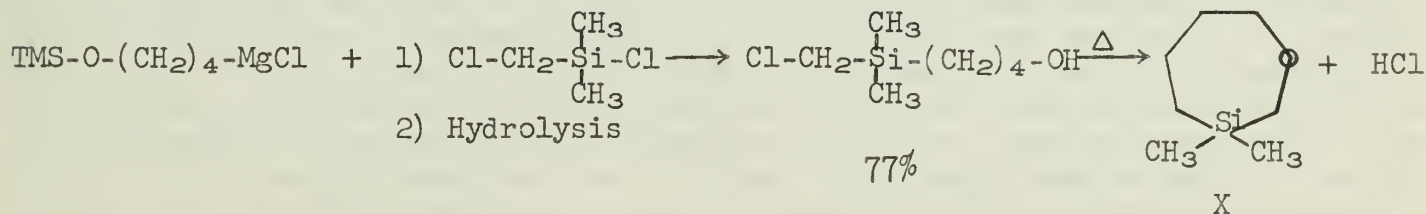


Alkyl organometallic reagents of IX (Li, Na, Mg) were also prepared. When X-2, ethylene was formed and when X-3, Mg was found to be unreactive. In the

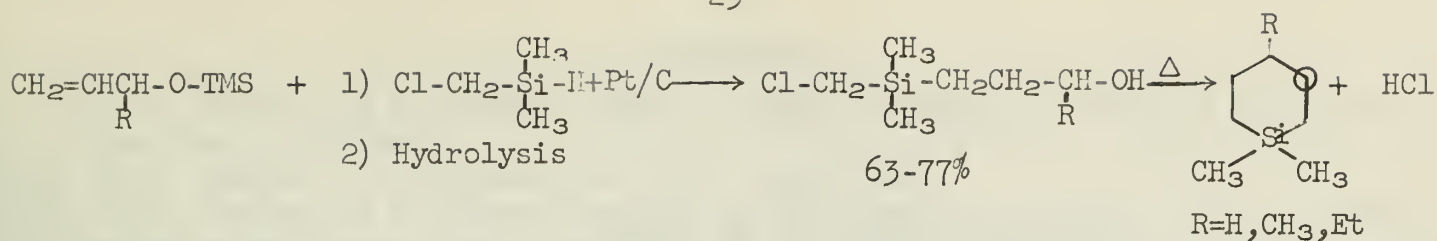


case of X-4,5, stable organometallic reagents were formed which Speier feels would be useful in organic synthesis for introduction of a hydroxyl group on the end of the chain into any molecule capable of coupling with a Grignard.

Reaction of the Grignard of IX (X-5) with HgCl_2 followed by hydrolysis gave $\text{HO}-(\text{CH}_2)_5\text{HgCl}$ in 86% yield. Fessenden²⁴ used the Grignard reagent of IX (X-4) as an intermediate in the preparation of 3,3-dimethyl-3-sila-1-oxacycloheptane, X.

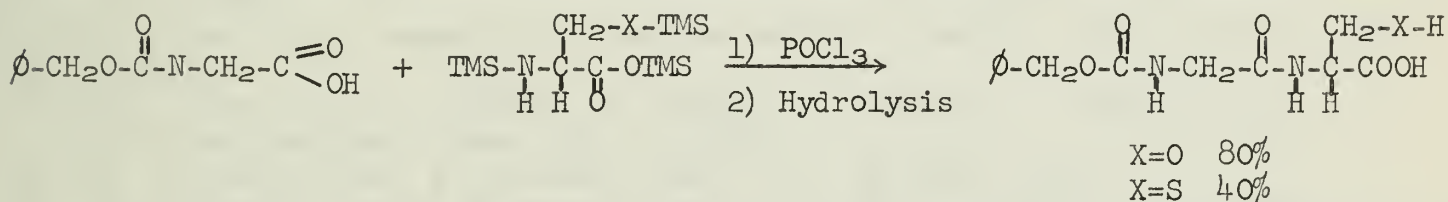


In another synthesis, Fessenden²⁵ employed α -substituted, TMS blocked allyl alcohols in preparation of a series of heterocyclic compounds XI.



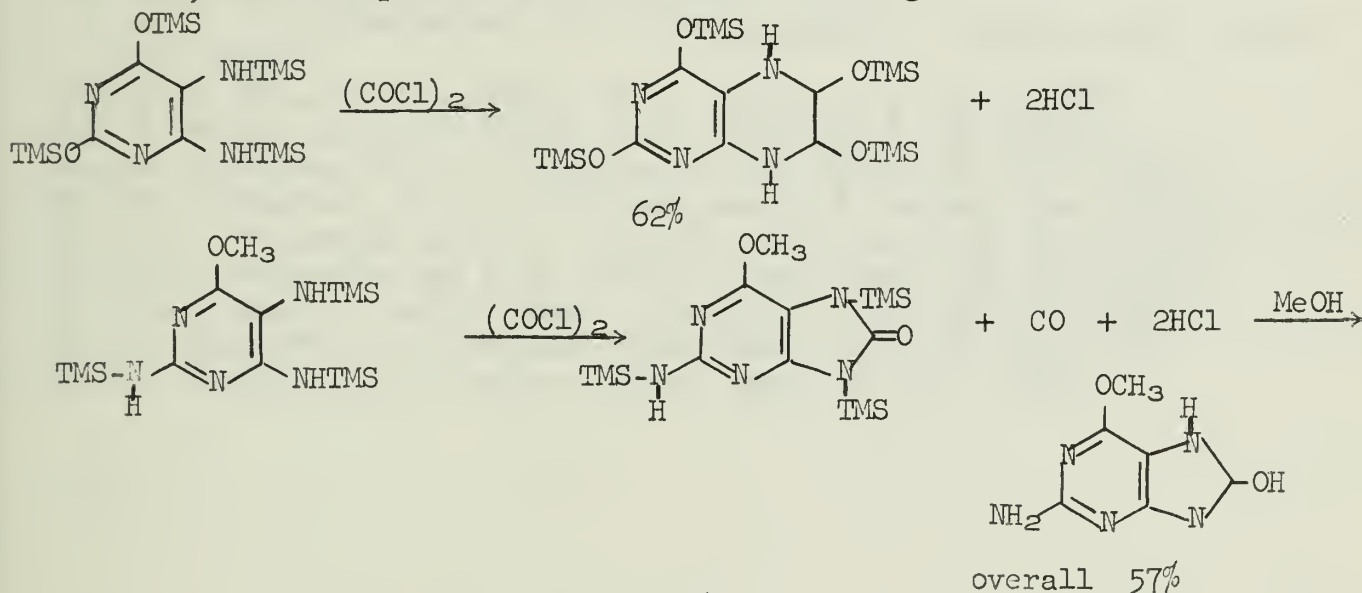
XI

Henglein and Knoch²⁶ prepared TMS derivatives of amino acids in 1959 and in 1961, Birkofer, and others,³ utilized TMS substituted acids, alcohols, thiols and amines in the syntheses of di- and tripeptides. By using TMS as a blocking group, Birkofer was able to protect three sites simultaneously (-NH₂, -OH or -SH, -COOH) without affecting the ability of the amine group to react. All three blocking groups were removable in a single hydrolysis step as illustrated in the following equation:



Birkofer also has used TMS derivatives in the synthesis of disaccharides.⁷ Treatment of 1,2,3,4-tetrakis-O-(TMS)-D-glucose with tetra-O-acetyl-α-D-glucopyranosyl bromide followed by hydrolysis yielded 2', 3', 4', 5'-tetra-O-acetyl-gentiobiose.

Substituted purines and pteridines²⁷ have been prepared through TMS intermediates, some examples of which are the following:



SUMMARY

The TMS group as a blocking agent for alcohols, phenols, amines, acids and thiols offers the advantage over most other blocking groups in that it not only adds the properties of thermal stability, low viscosity and resistance to oxidation but is also easily prepared and essentially quantitatively removed by hydrolysis. Application to VPC and separation procedures involving distillation along with use in organometallic synthesis and synthesis of biological compounds are some of the ways in which the TMS group has been utilized. The only disadvantages of the TMS group seem to be its restriction to use in nonhydroxylytic solvents and possible rearrangements in organometallic synthesis.

A review by Birkofer and Ritter²⁸ on the use of the TMS group in organic synthesis has recently appeared.

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THE OXIDATION OF NITROGEN CONTAINING COMPOUNDS WITH LEAD TETRAACETATE

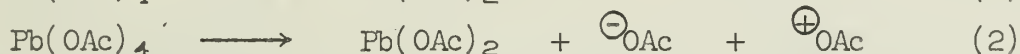
Reported by Hayden I. Lipp

July 7, 1965

INTRODUCTION

Since its introduction in 1920¹ as an oxidizing agent of organic compounds, lead tetraacetate (LTA) has found an increasing number of applications. Review articles^{2,3,4,5} have surveyed many of the reactions of LTA, however many newer and less common reactions have not as yet been reviewed. The scope of this seminar will be limited to those reactions of LTA involving the oxidation of nitrogen containing compounds.

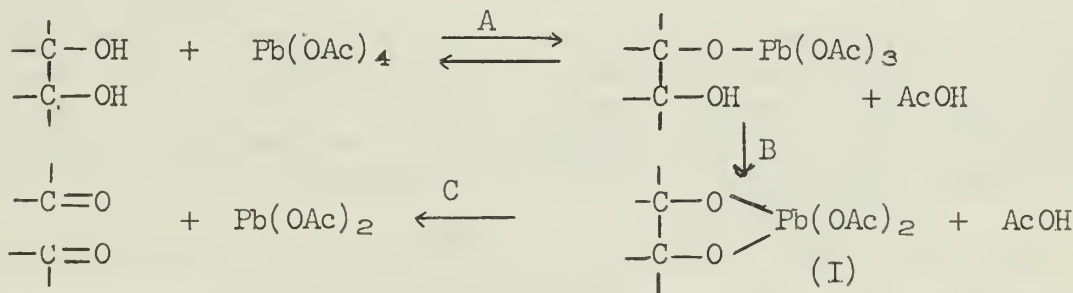
The oxidizing properties of LTA have been attributed to initial decomposition of the reagent to reactive intermediate species which subsequently attack the substrate, or attack by LTA itself to form an initial lead-substrate adduct. Equations 1 and 2 illustrate the two most probable modes of LTA decomposition.^{2a} In spite of the wide variety of mechanistic proposals, the question of homolytic or heterolytic reaction has remained unresolved in many cases. In part, this ambiguity arises from the unequivocal observation of both radical and ionic characteristics in reactions of LTA under different conditions. The high temperature methylation of aromatics,⁶ for example, is clearly a radical process, while the rearrangement observed during the oxidation of benzpinacolyl alcohol⁷ indicates the intervention of ionic intermediates. It is therefore not surprising that the LTA oxidations of nitrogen containing compounds is the subject of conflicting mechanistic proposals.



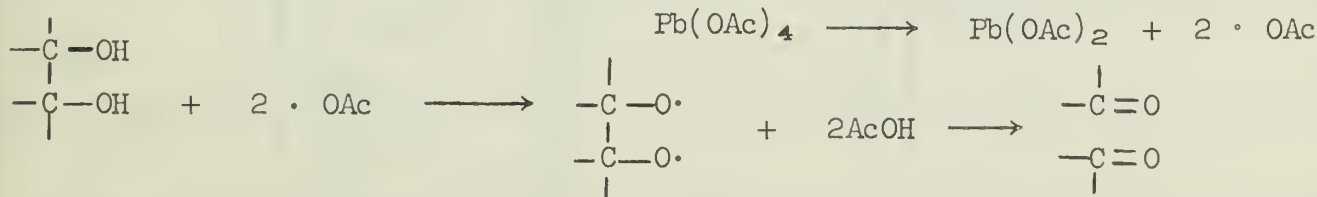
${}^{\oplus}\text{OAc}$ being the oxidizing species.

GLYCOLS AND AMINO ALCOHOLS

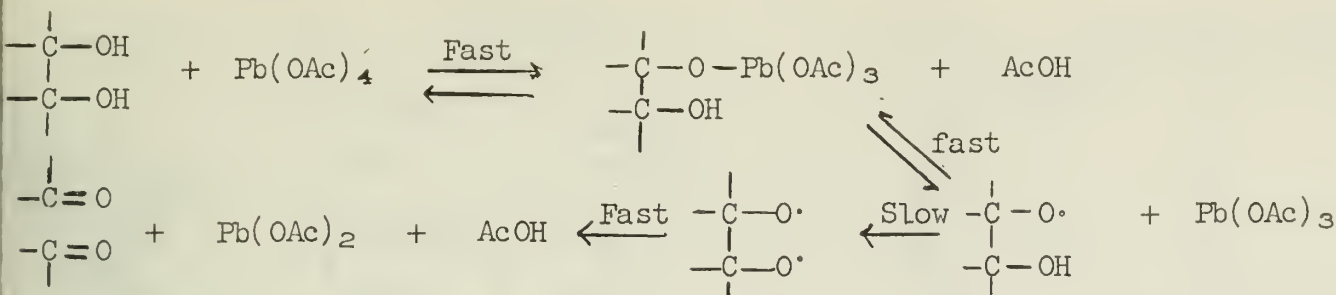
Of all the LTA reactions, glycol cleavage to form aldehydes and ketones is perhaps the best known. Criegee and co-workers first proposed a mechanism for this reaction in 1933.⁸ Their first interpretation proposed attack on the glycol by LTA to form the adduct I. Assuming that B is the rate determining step, this mechanism accounts for the observed kinetics in acetic acid (first order in LTA and glycol). It also accounts for the observations at that time that all cis glycols react faster than trans glycols. That step A is correct is supported by the formation of $\text{Pb(OAc)}_2(\text{OH})(\text{OMe})$ in aqueous methanol.



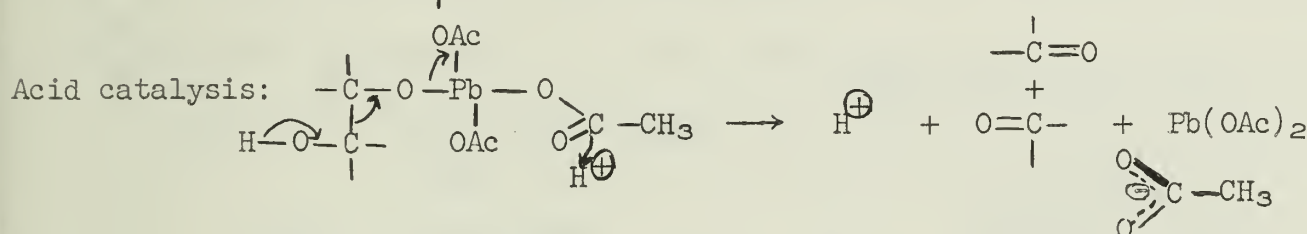
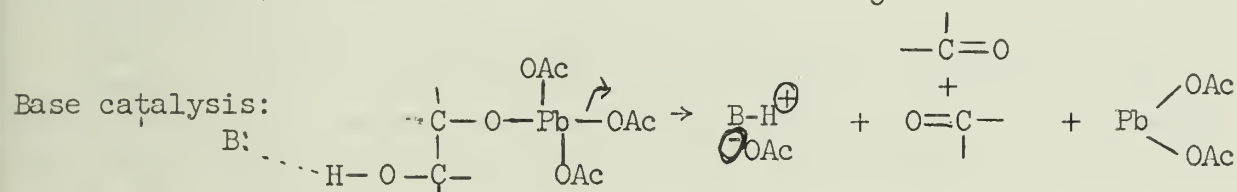
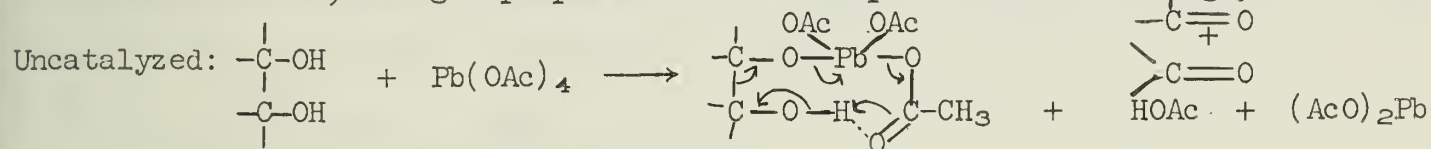
Later Waters⁹ proposed a free radical mechanism for the cleavage. This suggestion has been excluded by the observation that acetyl peroxide, which is known to give $\cdot\text{OAc}$ in solution¹⁰ does not cleave glycols.



A third mechanism was proposed later by Cordner and Pausacher.¹¹ It is a several step mechanism which shows many similarities to Waters'. This mechanism does not explain the stereochemistry and is untenable in the light of more recent data.



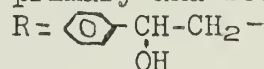
During the post-1933 period, new data was accumulated causing Criegee to modify his initial mechanism^{2a,12a}. The discovery of general acid^{12b} and base catalysis^{12a} ruled out both free radical intermediates, and intermediates of the type I. In addition, Criegee and co-workers^{12a} investigated many systems, notably fused rings, in which the trans isomer apparently reacted faster than the cis analog. To account for these observations, Criegee proposed the now accepted mechanism for glycol cleavage.






This concerted mechanism accounts for the observed kinetics if formation of the adduct is rate determining. It also accounts for acid and base catalysis and the observation that several rigidly trans fused glycols can react with LTA, and actually faster in many cases, due to the ease of approach of acid or base on the side opposite to the point of LTA attachment.

An -NH₂ or -NHR group is equivalent to an -OH group in rendering a compound oxidizable by lead tetraacetate.³ Thus α-diamines, α-amino alcohols, and α-amino acids can be oxidized with LTA via the same mechanism as glycol cleavage (except for tertiary amino groups). However, the expected imines R-CH=NH, usually undergo further reaction.^{13,14} Table I illustrates the various cleavage products from primary and secondary amino alcohols.¹³

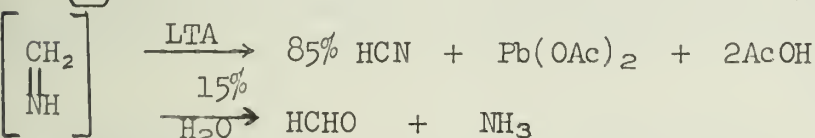
TABLE I.



1° Amino Groups				
Substrate	Products		Moles LTA consumed	
			Theory	Actual
R-NH ₂	C ₆ H ₅ CHO HCHO	NH ₃ HCN	1.0	1.85
 -CH-CH ₂ -OH NH ₂	C ₆ H ₅ CHO HCHO	NH ₃ C ₆ H ₅ CN	1.0	1.86
2° Amino Groups				
 -CH-CH ₂ OH NH-CH ₂ - 	C ₆ H ₅ CHO HCHO	NH ₃ Benzylamine C ₆ H ₅ CN	1.0	1.71

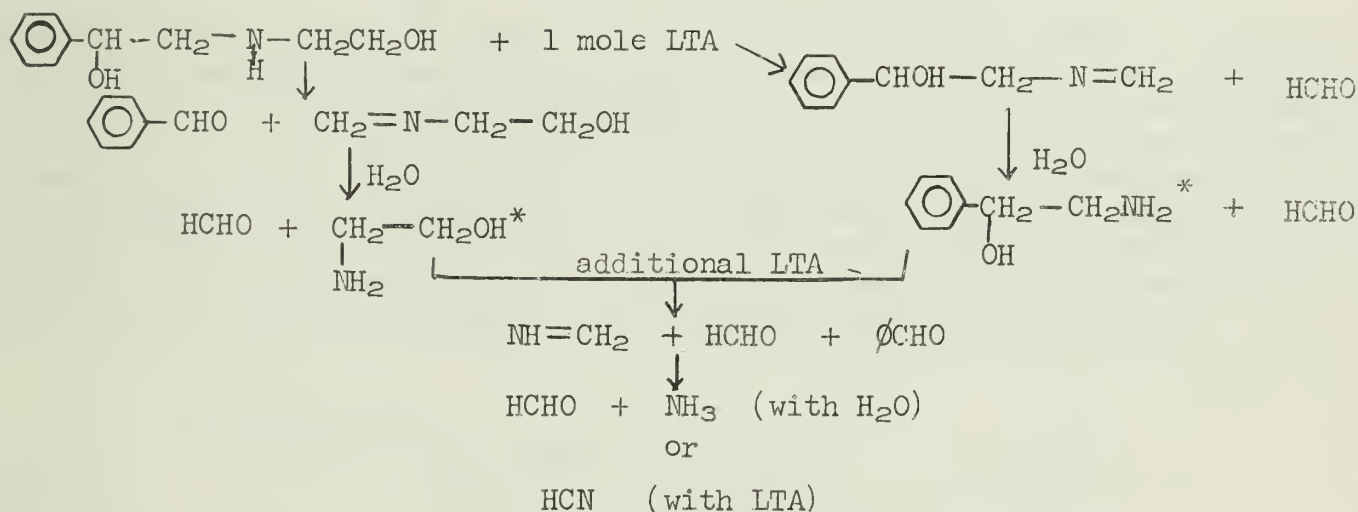
Substrate	Products		Moles LTA consumed	
			Theory	Actual
$\text{R}-\text{N} \begin{array}{l} \text{H} \\ \text{CH}_3 \end{array}$	$\text{C}_6\text{H}_5\text{CHO}$ HCHO	methyl aniline	1.0	1.21
$\text{R}-\text{N} \begin{array}{l} \text{H} \\ \text{CH}_2\text{CH}_2\text{OH} \end{array}$	$\text{C}_6\text{H}_5\text{CHO}$ HCHO	NH_3 HCN	2.0	2.87

The appearance of two nitrogen containing compounds, (NH_3 , or amine, and nitrile) can be rationalized as arising from different decomposition modes of the intermediate imine.



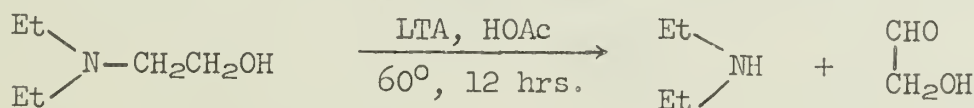
The dehydration of the imine explains

the consumption of more than the anticipated one mole of LTA. In the above example, 85% conversion to HCN corresponds quite well with the experimental observation of 1.85 moles consumption of LTA. If one restricts the amount of LTA to exactly the theoretical calculated quantity, the reaction can be limited to the formation of amine or ammonia.



* These are the only nitrogen containing compounds isolated when LTA is restricted to only one mole. With LTA in excess of 1 mole, the reaction proceeds as indicated.

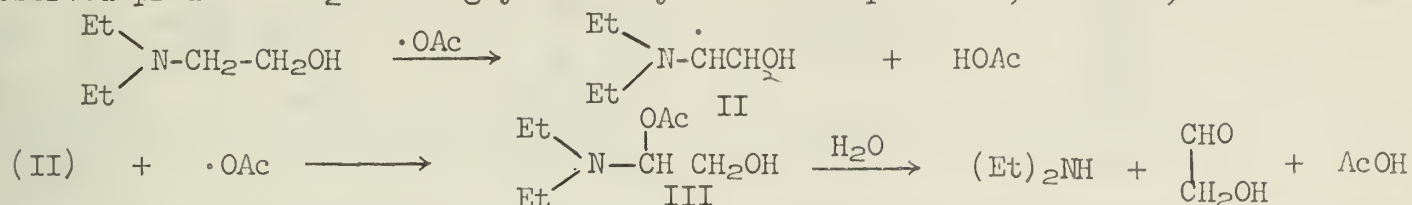
The analogous reaction with tertiary amino groups is not as well understood. Leonard and co-workers¹⁵ observed that LTA in glacial HOAc at 60° is not specific for 1,2-tertiaryamino alcohols, since 3-diethylamino-1-propanol and 4-diethylamino-1-butanol were both oxidized, although at a slower rate than the 1,2 compound. Leonard also observed the production of secondary amines in all cases studied and glyoxal in those cases where the other fragment could be isolated without decomposition. Therefore, he concluded that the tertiary amino alcohols must undergo cleavage in the C-N



bond. In short, the LTA oxidation of tertiary amino alcohols at 60° represents a different reaction from the LTA oxidation of glycols, or of primary or secondary amino analogs at 25°, which undergo only C-C cleavage.

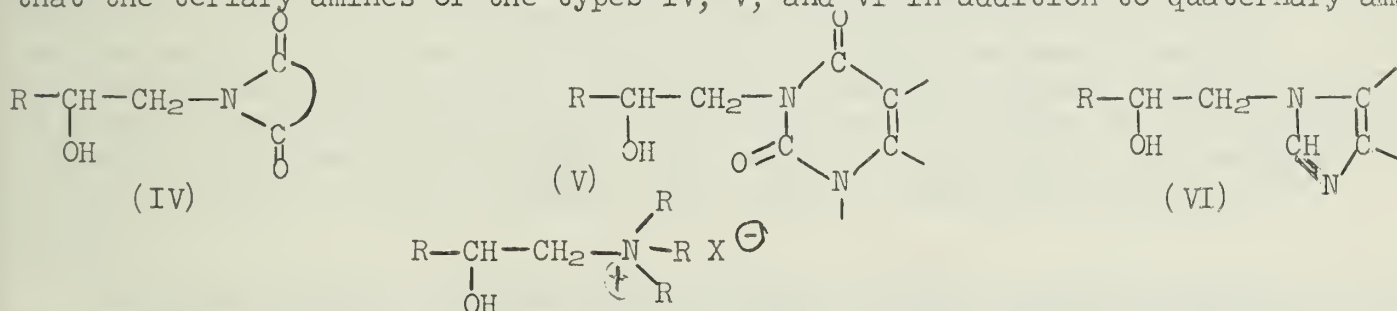
It is known that LTA in hot glacial acetic acid furnishes the acetoxy free radical.¹⁶ Leonard proposed that the reaction of LTA with 2-diethylaminoethanol, for example, may involve the removal of a hydrogen radical from the carbon bearing the diethylamino group to form HOAC and the free radical II. This radical could combine with $\cdot\text{OAc}$ to

form 1-diethylamino-2-hydroxyethyl acetate (III). Formation of III accounts for the observed consumption of only one mole of LTA. The hydrolysis of III would produce the observed products Et_2NH and glycolaldehyde. It is possible, however, that if this

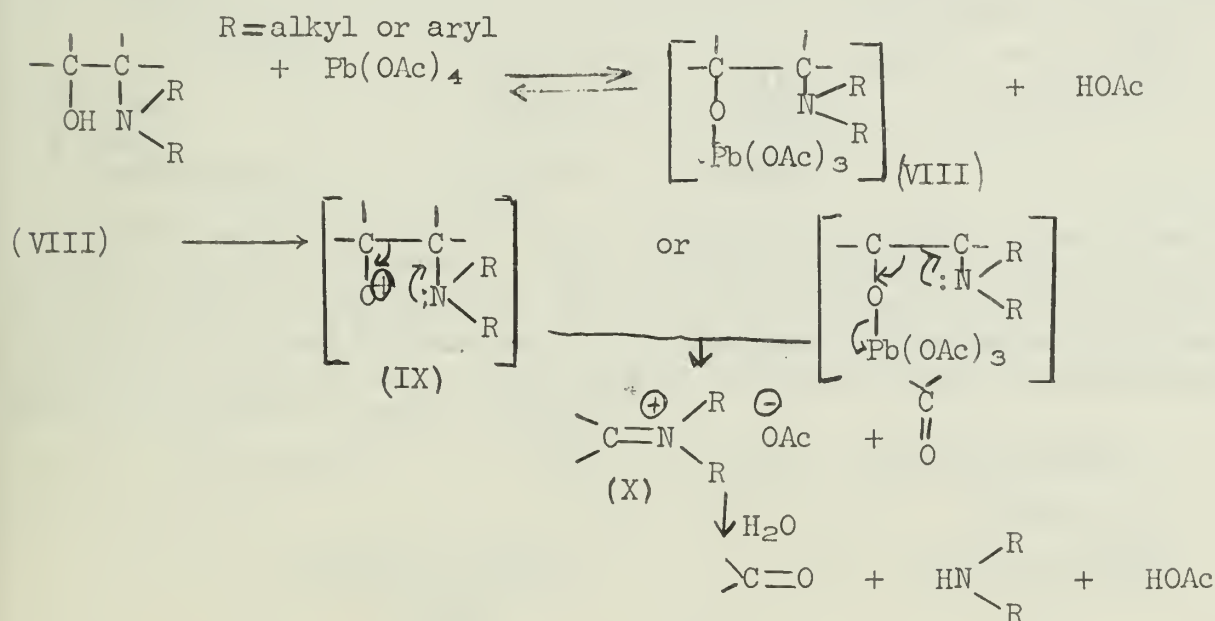


reaction could be conducted at 25° , it would follow a different mechanistic path paralleling simple glycol cleavage. Several other examples^{17,18} of LTA oxidations which take an alternate course at different temperatures with the same substrate are known.

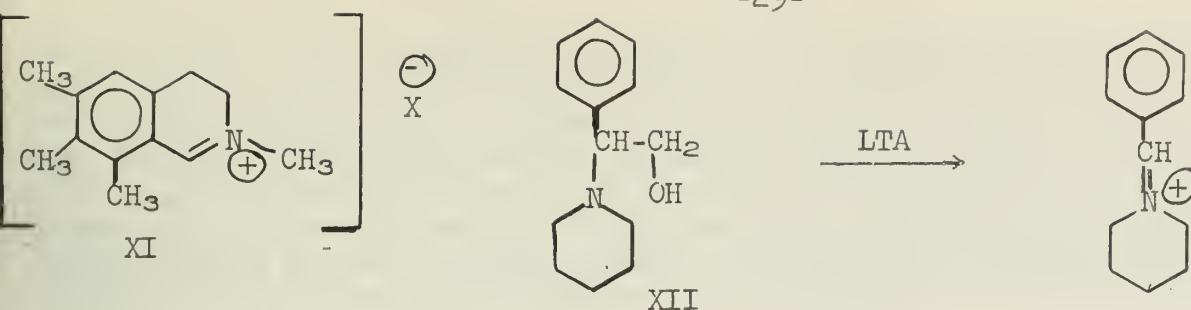
Roth and co-workers^{13,19} later proposed a mechanism for the cleavage of tertiary amino alcohols related to the cleavage of primary and secondary amines. They found that the tertiary amines of the types IV, V, and VI in addition to quaternary ammonium



salts VII, do not undergo cleavage. From these observations, these workers concluded that a free electron pair is necessary for reaction. Compounds of the types IV, V, and VI, do not have totally "free" electron pairs, due to electron withdrawal by the carbonyl and double bond functions. Type VII compounds have the electron pair missing. This electron pair dependence can be rationalized by the following mechanism. It is proposed that the initial adduct VIII is identical to that obtained in the primary and secondary case. This intermediate can either lose $\text{Pb}(\text{OAc})_2$ and OAc^- to form IX or can react via a concerted mechanism to form the immonium salt directly, which can then decompose to the corresponding secondary amine.



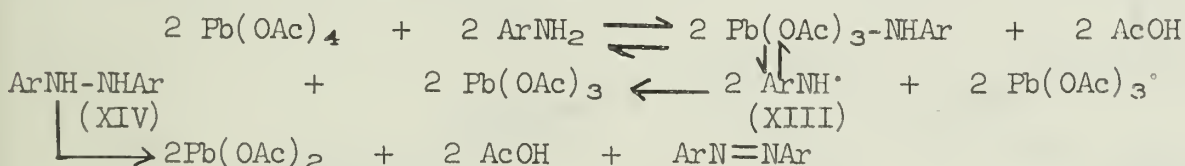
In order to prove their mechanism, Roth and co-workers attempted to isolate a stable immonium salt from the reaction. Immonium salts in which the nitrogen double bond is conjugated with a benzene ring XI are known to be stable. When Roth employed XII as the substrate a stable immonium salt was produced.



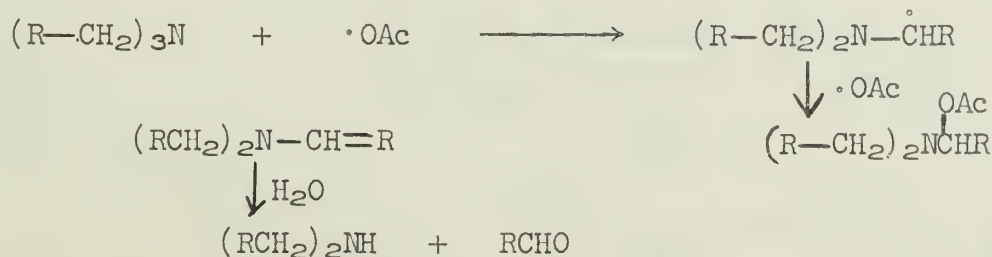
The isolation of this stable salt was taken by Roth as proof of his mechanism. However, he neglected to comment on the earlier work done by Leonard, and did not attempt to rationalize the formation of glyoxal and the reaction of 1,3 and 1,4 amino alcohol isomers. Both workers used approximately the same experimental conditions. Considering that Roth did not obtain immonium salt in quantitative yield, and that Leonard did not isolate the theoretical amount of glyoxal, it is possible that the two reaction mechanisms are competitive, and that both pathways are available for reaction. This would also account for the rapid decrease in rate as one goes from 1,2 to 1,3 to 1,4 isomers and the portion of the reaction attributable to Roth's mechanism vanishes. Although this may appear to be a logical compromise, it does not account for the absolute failure of certain types of tertiary amino groups to react, for there is no "electron pair" restriction on Leonard's mechanism. The correct interpretation of tertiary amino alcohol cleavage is indeed complex, and as yet not completely resolved.²³

AMINES

The first amines investigated were primary aromatic amines (aniline and substituted anilines).^{21,22} Pausacker and Scroggie²¹ found that the action of lead tetraacetate on these amines produced azo-compounds, although the yields varied widely--from 5% with aniline to 56% with 3-chloroaniline. Pausacker and Scroggie proposed a mechanism in which the LTA initially adds to the amine and the adduct homolytically decomposes to the free radical XIII. This radical may dimerize to XIV which eventually leads to the azo-product, or react in other ways to form side products which supposedly accounts for the poor yields of azo-product. Pausacker and Scroggie also investigated α - and β -naphthylamine, neither of which gives azo-coupling products on treatment with LTA. Only 1,4-naphthaquinone (16%) was obtained from α -naphthylamine, while β -naphthylamine gave a complex mixture from which 1,2,6,7-dibenzophenazine (3%), 2-amino-1,4-naphthaquinone (25%) and 2-acetamino-1,4-naphthaquinone-1- β -naphthylamine anil (60%) were isolated.

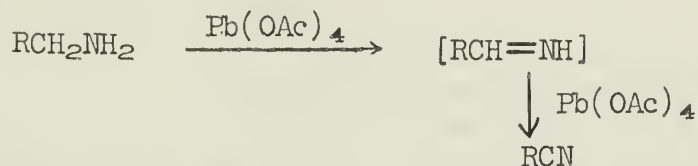


Horner and co-workers²³ later investigated tertiary amine oxidation by LTA in the presence of acetic anhydride. This reaction apparently proceeds by $\text{H}\cdot$ radical abstraction by $\cdot\text{OAc}$, and addition of $\cdot\text{OAc}$ to the carbon bearing the nitrogen. This is followed by loss of HOAc and hydrolysis to the aldehyde and the amine which becomes acylated and doesn't react further. This mechanism bears a striking resemblance to that proposed by Leonard for amino alcohols.



Recently primary unbranched aliphatic amines have been investigated,²⁴ and give nitriles on treatment with LTA. The reaction may proceed through an unstable aldimine formed by dehydrogenation. This is similar to the mechanism for tertiary amines, which dehydrate to form a C-C double bond, probably because C-N double bond formation would

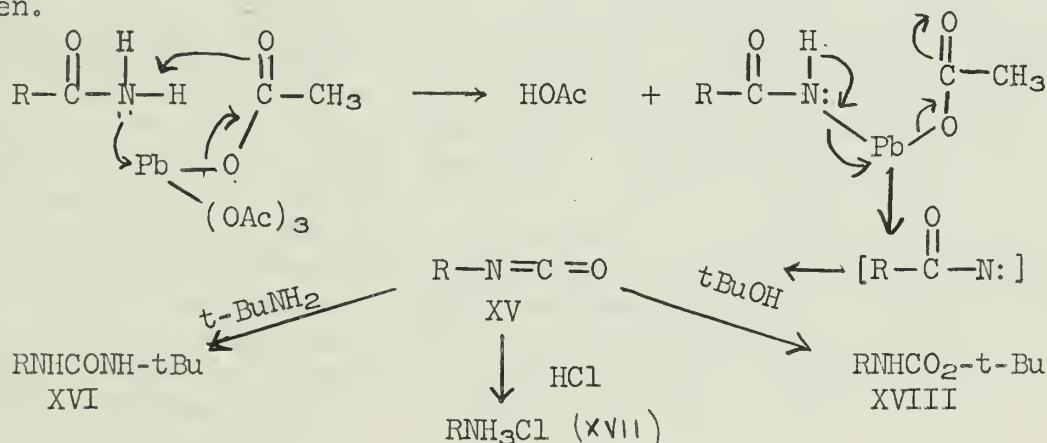
be difficult. In the case of benzylamine, the obtained benzonitrile was accompanied by a small amount of benzaldehyde (2-4%), which probably arose from hydrolysis of the intermediate benzaldimine. A radical mechanism is supported by the lack of acid or base catalysis, and the isolation of benzyl acetate (albeit in low yield), resulting from attack of methyl radicals (generated by the decomposition of acetoxy radicals formed from LTA in the course of the reaction) on the solvent benzene. None of the minor products isolated could be traced to oxidative coupling (hydrazines) or intramolecular cyclization (pyrrolidines or piperidines).



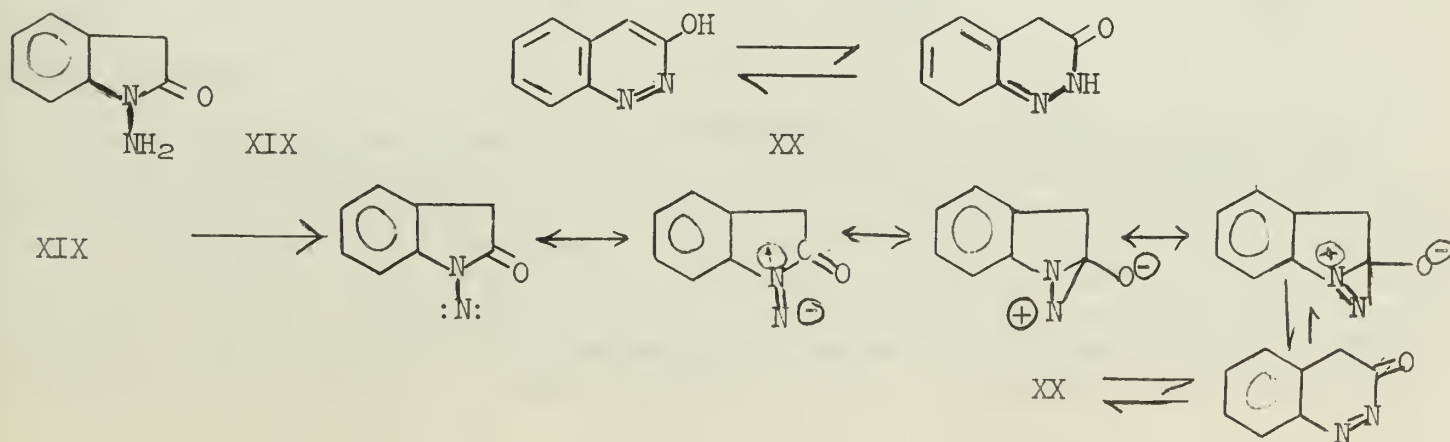
The reaction with secondary amines has not been studied, but Coppinger and co-workers⁴⁰ have investigated the action of t-BuOOH on amines, and obtained results for this reaction that are comparable with the LTA oxidations for primary and tertiary amines. Coppinger and co-workers also investigated secondary amines, and observed dehydrogenation products similar to those obtained in the first step of the primary amine reaction ($\text{RCH=N-CH}_2\text{-R}$ from $(\text{RCH}_2)_2\text{-NH}$). By analogy, secondary amines can be assumed to react in the same manner with LTA.

AMIDES

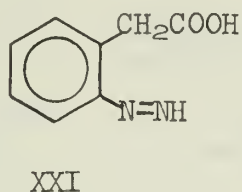
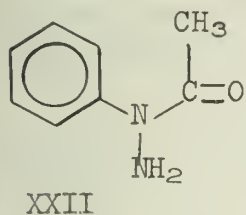
Baumgarten and co-workers²⁵ have reported an oxidative rearrangement of amides that yields products similar to those obtained from the Hofmann rearrangement. They converted a number of aliphatic and aromatic amides into the corresponding isocyanates XV, and their derivatives XVI, XVII, XVIII. The proposed mechanism is similar to those mentioned previously,³ and consists of initial attack to form the lead-substrate adduct which decays concertedly to the nitrene and then to the observed products. Base catalysis has been observed. Presumably the base aids in the removal of the hydrogen.



Baumgarten and co-workers also investigated the effect of LTA on N-amino amides.²⁶ Neber's lactam XIX was converted to 3-cinnolinol (XX) upon treatment with LTA in dry benzene. This reaction may proceed through the same type of nitrene intermediate.



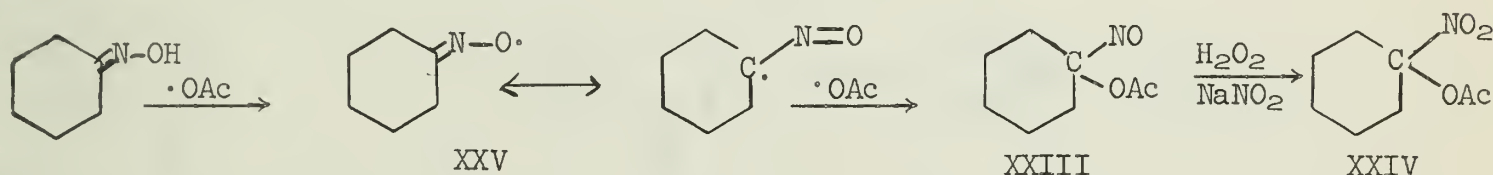
Neber's lactam could be considered analogous to an α -amino ketone in which the α carbon has been replaced by nitrogen. This cleavage should lead to an acid and an aryl diimine, or in this case, *o*-carboxymethylphenyldiimide (XXI), which could cyclize to XX. This mechanism must be discarded however, since very little benzene was obtained from the oxidation of the analogous compound XXII. The unstable intermediate phenyldiimide should be formed from XXII by this mechanism, and then decompose to benzene and nitrogen.



OXIMES

Iffland and Criner published the first communication on LTA oxidations of oximes in 1956.⁴¹ They oxidized cyclohexanone

oxime with LTA at 5° C and isolated a blue oil (indicative of N=O compounds), for which they postulated the structure XXIII, which they oxidized to XXIV. The intermediate XXIII could arise by abstraction of a hydrogen radical, and resonance of the free electron through a π system, placing electron density on the carbon, at which point combination with another $\cdot\text{OAc}$ could take place. As shown later, this is not quite correct.



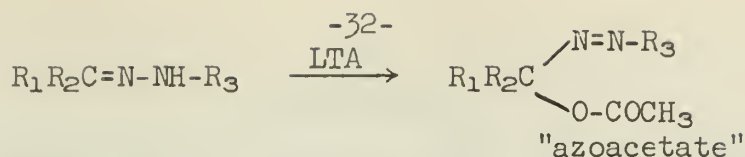
As proof of structure XXIV, Iffland and Criner relied on an elemental analysis and hydrolysis of XXIV to cyclohexanone and HOAc, indicating that the nitro and acetoxy groups must be on the same carbon.

Since Iffland and Criner's early work, several workers have been concerned with the existence and structure of the proposed "iminoxy" free radical.²⁷⁻³⁰ Lemaire and Rassat,^{27,30} working with LTA, and others working with different oxidizing agents,^{28,29} found a nitrogen hyperfine constant on the order of 30 gauss in the ESR spectra. They also observed *syn* and *anti* isomers of the radical in equal amounts, regardless of the configuration of the initial oxime. These facts preclude a π allylic type radical XXV which would be symmetric and not show *syn* and *anti* isomers, and which would exhibit a much smaller nitrogen coupling constant. The alternative structure is a σ type, in which the radical is formed in a p orbital but hybridizes into an sp^2 orbital, situated in the plane of the molecule, not above it. The electron is localized principally on the nitrogen atom and is associated with the oxygen through a σ , sp^2 orbital XXVI. This is analogous to NO_2 ,³¹ and accounts for the high nitrogen splitting constant. It is then possible to comprehend the dissymmetric electronic environment of the hydrogens. Rotation about the C-N double bond is hindered, and the hydrogens are in different environments. This is analogous to the vinyl radical, where two different hydrogens are seen.³²

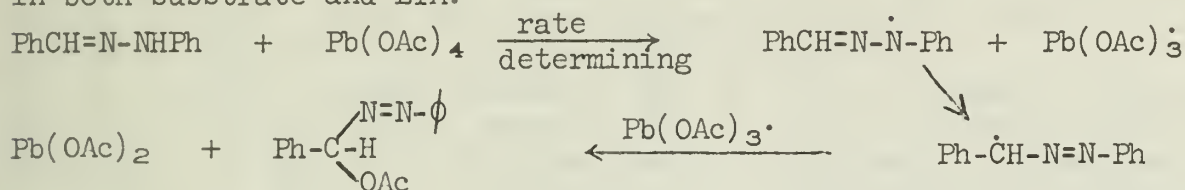


PHENYLHYDRAZONES

While investigating oxime reactions,²⁶ Iffland and co-workers examined the reaction of cyclohexanone phenylhydrazone, and isolated an "unidentifiable" oil. Later examination³⁷ has shown that this oil is an "azoacetate," a previously unknown class of compounds. The "azoacetate" reactions are simple, produce high yields, and are not contaminated with by-products. The course of the reaction is not affected by variation of alkyl, cycloalkyl, or phenyl substituents on the carbonyl carbon, or by varying R_3 . The structure of the azoacetate obtained from hydrazones in the LTA reaction is similar to the auto-oxidation product from the treatment of benzaldehyde

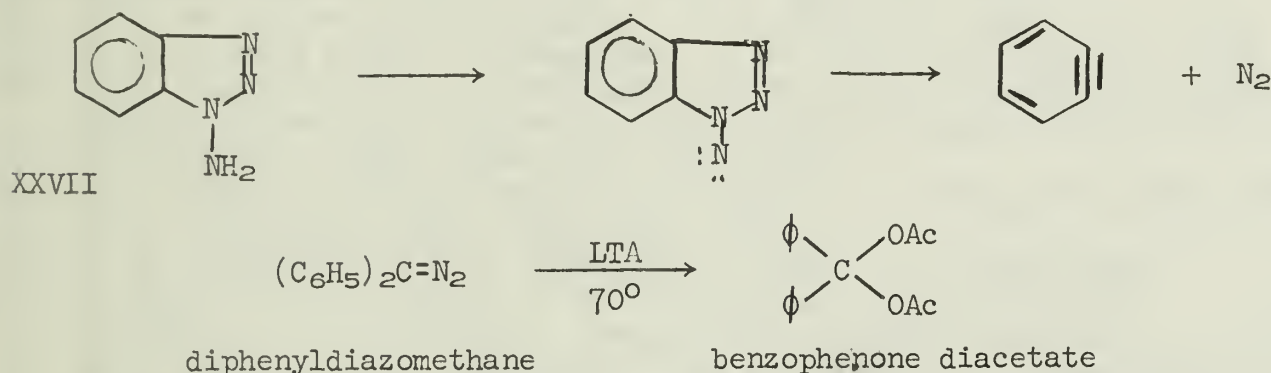


phenylhydrazone with O_2 from azohydroperoxides,³⁸ and probably proceeds via the same mechanism. Kinetic studies indicate the reaction is first order in both substrate and LTA.

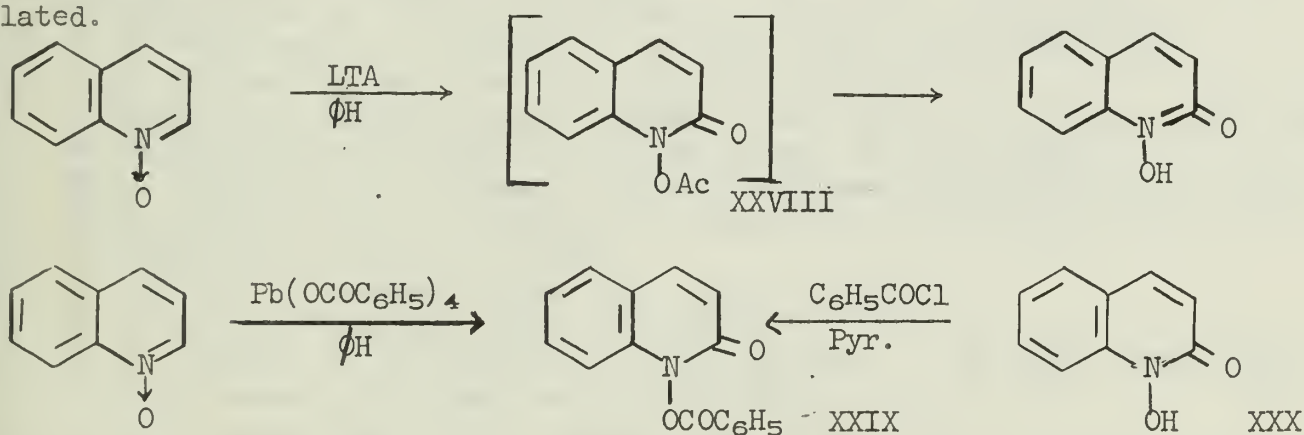


MISCELLANEOUS

There are several other, lesser known reactions of LTA with nitrogen compounds which will not be covered in detail here. They include the reaction of XXVII with LTA to form the nitrene intermediate, and then benzyne, which can be trapped in a conventional manner;³³ the oxidation of formazyl derivatives;^{34,35} and the reaction with diazomethane derivatives to form the acetoxy adducts.³⁶



Quinoline oxides also react with LTA³⁹ in a reaction scheme outlined below. The proposed intermediate XXVIII has not been isolated from among the oxidation products with LTA, however $Pb(OCOC_6H_5)_4$ gives XXIX. As additional proof of this mechanism, the product XXX can be treated with C_6H_5COCl in pyridine, and the intermediate benzoate isolated.



SUMMARY

It has been shown that there are a variety of reaction mechanisms possible for the oxidation of nitrogen containing compounds with lead tetraacetate. However, the two most probable mechanisms for this particular aspect of lead tetraacetate chemistry are free radical and concerted processes, and the anionic/cationic mechanism(2) - important in other systems - does not seem to be operative here.

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THE PHOTOCHEMICAL CONVERSION OF STILBENE TO PHENANTHRENE

Reported by Robert J. Schacht

July 14, 1965

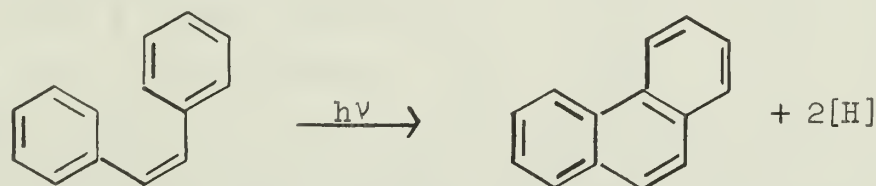
INTRODUCTION

The realm of photochemistry is only now beginning to reveal its potential in both theoretical and practical application in the field of organic chemistry. While large quantities of empirical data have been gathered, relatively few reactions have received the precise characterization essential for development of the unified understanding prerequisite for the significant utilization of the techniques to industrial and biological processes. With this in view, the photochemical conversion of stilbene derivatives to phenanthrenes becomes significant as it has received considerable attention in attempts to characterize the mechanism of the reaction definitively.

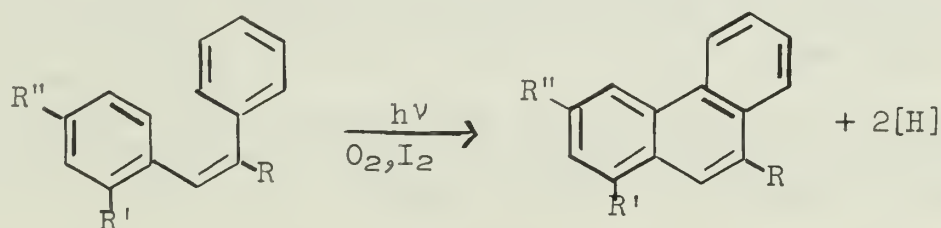
ABSTRACT

While the photochemical isomerization of trans-stilbene systems to cis-stilbene systems has been known for some time, only recently has the competing cyclization reaction to phenanthrene been articulated. In 1934, A. Samkula,¹ while studying the cis-trans isomerization of stilbene, observed anomalous ultraviolet absorption in the reaction solutions containing cis-stilbene. G. N. Lewis² concurred in this observation some years later, also noting that trans-stilbene solutions gave an apparently similar ultraviolet absorption spectra upon prolonged irradiation. Aside from a brief communication, devoid of chemical and spectral data, suggesting that the unknown product was phenanthrene,³ the problem remained dormant until 1955 when R. E. Buckles performed extensive investigations.

Buckles⁴ discovered that upon irradiation, cis-stilbene in solution ($5 \cdot 10^{-5}$ M. in cyclohexane, ethyl alcohol, and acetonitrile) was converted in up to 95% yield to a new product whose spectral qualities were essentially identical with those of phenanthrene. Long term irradiation periods (twenty days) of more concentrated cis-stilbene solutions (0.2 M. in ethanol) allowed the isolation and chemical characterization of phenanthrene.



Since this work, a large number of stilbene derivatives and analogues have been shown to undergo this type of photochemical conversion to give variously substituted phenanthrenes. The following reactions give an example of the scope of this reaction.¹⁸



With the elucidation of the structure of the reaction product and the apparent wide applicability of the reaction's synthetic utility, mechanistic studies became quite in order.

The reaction of the stilbenes is at least formally analogous to the photochemically induced cyclization of 1,3,5-hexatriene - hence a suitable point of departure. R. Srinivasan^{5,6} has irradiated an equal mixture of the cis- and trans-1,3,5-hexatriene in the vapor phase and has isolated the following components of the reaction mixture: 1,3-cyclohexadiene, benzene, hydrogen, and small yields of degradation and rearrangement compounds. The reaction demonstrated a distinct decrease in rate as the reactant vapor pressure was increased above 8 mm. Hg or when non-reactive gases were added to the reaction medium. Furthermore, the

starting material isolated from the reaction mixture possessed a markedly increased ratio of cis to trans isomer after both low and high conversions. On the basis of these limited data, Srinivasan postulated that the reaction occurred through the cis isomer, the trans being isomerized to the cis prior to cyclization. The dampening effect of the diluent gases was interpreted to be a result of a cyclization originating from a vibronically excited ground state derived from the interconversion of the initially formed excited singlet state.

Unfortunately, the solution photocyclization of the unsubstituted triene has not been accomplished. G. J. Fonken⁷ has been able to cyclize compounds as closely analogous as the 1,6-dimethyl derivative but has wholly failed with the triene itself. No explanation has been forthcoming for this. J. L. M. Schlattmann and E. Havinga⁸ have found this type of reaction to be extensively utilized in the bio-synthesis of vitamin D, its intermediates, and related compounds.

The stilbene system, as well, readily undergoes photocyclization in the vapor state in a reaction studied by Srinivasan^{9,10} as a natural extension of his previous work. In this study, cis-stilbene at a vapor pressure of 5 ± 0.5 mm. Hg was irradiated at 170°C . and the resulting products analyzed with vapor phase chromatography. In various subsequent reactions, external gases were bled into the reaction vessel prior to irradiation. The following is a tabulation of the resulting data:

Run	Time (min.)	Gas Added-	Phenanthrene - Rate m/min 10^{-2}	Final cis/trans
1.	60	-----	5.31	0.15
2.	120	-----	3.72	0.25
3.	65	O ₂ , 18.6 mm.	3.08	0.12
4.	60	O ₂ , 14.8 mm.	5.85	0.13
5.	60	O ₂ , 35.2 mm.	5.31	0.14
6.	60	Et ₂ O, 176.0 mm.	3.72	0.15
7.	120	Et ₂ O, 704.0 mm.	3.56	0.16
8.	120	C ₆ H ₁₂ , 372.0 mm.	3.19	0.16
9.	120	NO ₂ , 6.20 mm.	2.18	0.26

The production of phenanthrene was used as the criterion for the reaction's progress as conversions of extended duration with low intensity irradiation gave a hydrogen yield of 12 - 20% of that of phenanthrene; this was accounted for in the appearance of polymeric material. On the other hand, high intensity irradiations and short term conversion periods gave, within experimental error, equal yields of phenanthrene and hydrogen. Control reactions run with no irradiation gave quantitative recovery of starting material in the case of both oxygen/cis-stilbene and oxygen/phenanthrene charges.

The ring closure to phenanthrene from cis-stilbene was also found in a pyrolysis reaction at 550°C . Under these conditions a product mixture consisting of yields of 40% hydrogen, 40% phenanthrene, 10% trans-stilbene and polymeric material, was obtained.

In attempting to rationalize these data, Srinivasan considered two reaction mechanisms, one involving a concerted mechanism analogous to that of the 1,3,5-hexatriene system whereby cyclization and hydrogen elimination occur simultaneously; the other scheme involving the formation of a 11,12-dihydrophenanthrene intermediate (I) which possesses a discrete lifetime and which subsequently loses hydrogen spontaneously to form phenanthrene. A stepwise elimination of hydrogen was excluded since presumably the resulting free radicals would be trapped by the added oxygen and/or the added nitric oxide; no such effect was observed.

Srinivasan favored the former concerted mechanism since no intermediate was observed to accumulate in the system and since the reaction also occurred thermodynamically where "a highly strained intermediate (as I) is unlikely to be formed."

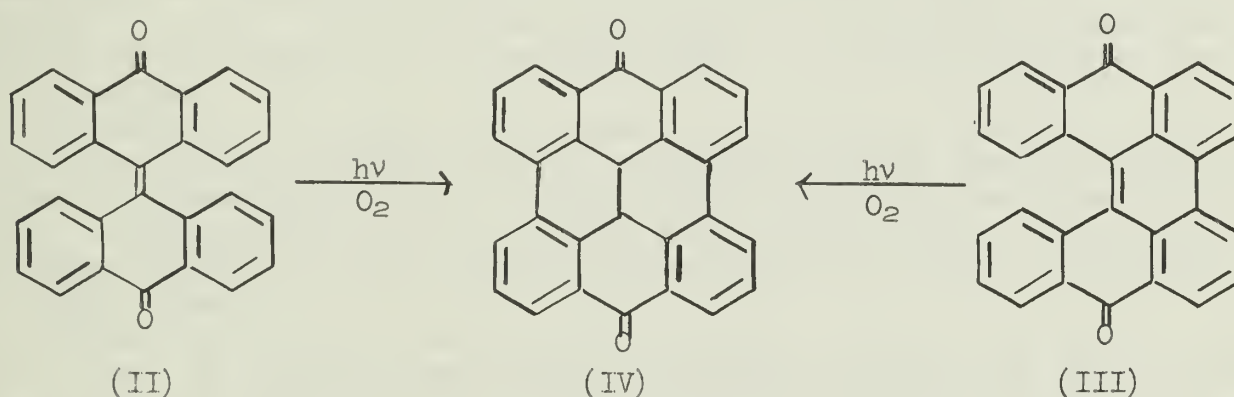
This reasoning deserves some question, however. The reaction need not necessarily proceed through the same mechanism in both the photochemical and thermochemical modes of induction; it is possible, however, that the relatively low energy of strain could be insignificant in view of the high energies of activation involved in the reaction. The point is somewhat academic, however, in view of the absence of observation which indicates a fleeting existence at best.

The absence of a rate reduction with the admixture of non-reactive gases gives credence to a mechanism where the reaction occurs through the first excited singlet state (S_1) rather than by means of the internal conversion of the electronically excited state to the vibrationally excited ground state felt operable in the 1,3,5-hexatriene case. The short lifetime of the S_1 state would preclude any appreciable vibrational energy loss in the pressure ranges utilized, whereas such an effect would be expected if the reaction were to proceed by an intersystem crossing mechanism to the longer lived excited triplet state (T_1).

To draw analogies from dilute gas phase reactions, as above, to solution reaction mechanisms is a most tenuous procedure since solvation and energy dispersion effects in the latter have little parallel in the former. Similarities may exist between the two forms of reaction, but conjecture can play little part in their verification.

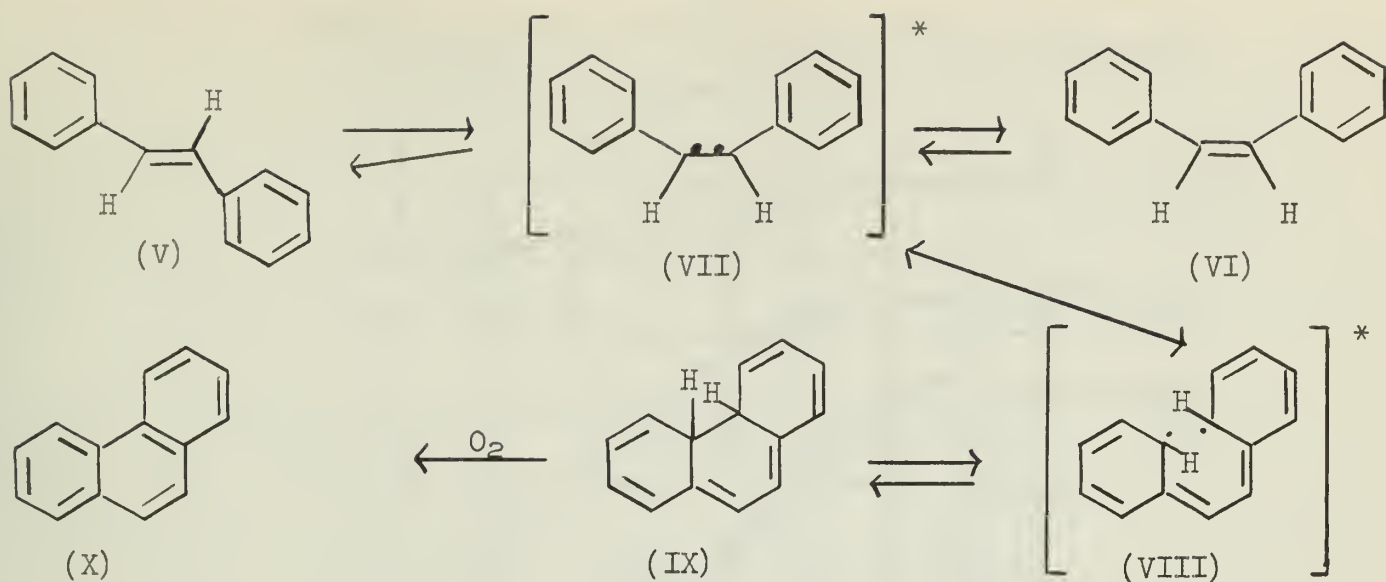
As the stoichiometry of the solution reaction is $C_{14}H_{12} \xrightarrow{h\nu} C_{14}H_{10} + 2(H)$, an obvious problem in characterization was the fate of the two moles of hydrogen eliminated; several laboratories independently determined that molecular oxygen, dissolved in the reaction medium, accounted for the hydrogen removal.

Although somewhat afield of the present discussion, H. Brackmann and R. Muhlmann¹¹ must be given some credit as the discoverers of this phenomena since they observed that the photochemical transformation of $\Delta^{10,11}$ -dianthrone (II) and helianthrone (III) to meso-dinaphthodianthrone (IV) required molecular oxygen, 0.8 - 1.0 moles per mole of hydrogen theoretically produced. This apparently occurred by the formation of hydrogen peroxide, which they found in the reaction solution.



Somewhat more to the point, P. Hugelshofer, J. Kalvoda, and K. Schaffner¹² observed the direct dependence of the stilbene photocyclization on oxygen. Upon irradiation of dilute trans-stilbene solutions under air, they were able to establish that 0.915 moles of oxygen were consumed per mole of isolated phenanthrene. Furthermore, with reactions run under pure oxygen, phenanthrene concentration reached a maximum after a one hour irradiation period where the same reaction required seven hours to reach this point under air. In this case, however, oxygen uptake continued well beyond the theoretical amount as large scale side oxidations became the dominant factor. On the other hand, reactions run under nitrogen atmosphere, with no reported attempt at prior degassing of the reactants, gave a concentration of phenanthrene only one-third that of the reaction under air after an otherwise identical seven hour irradiation.

With these somewhat meager data and noting that their product mixture contained considerable quantities of the cis-stilbene isomer, these researchers proposed a possible mechanism for the solution photocyclization:

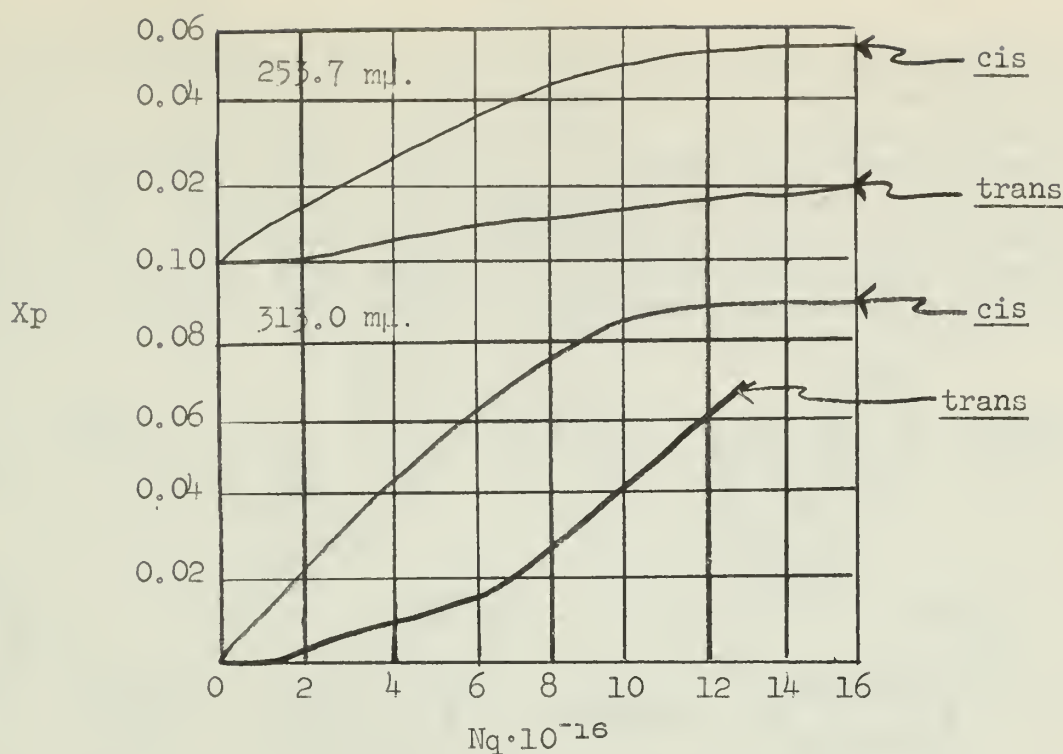


Although having neither evidence nor precedent for the dihydrophenanthrene intermediate (IX), they felt that its presence could be justified by the apparent rate effects of the different oxygen concentrations. In the case of the inert atmosphere, they theorized that some disproportionation reaction had occurred, an intermediate or stilbene itself being reduced as the phenanthrene formed. Unfortunately, they were unable to isolate any such reduction product.

The proposed mechanism was soon challenged by H. Stegemeyer¹³ who, arguing from a contemplative point of view, questioned the validity of the postulate dihydrophenanthrene intermediate. He noted that such a structure necessitated the loss of aromatic character in two ring systems, a process made highly unfavorable by the commensurate loss of resonance energy. Furthermore, he felt that in the absence of a precedent for dehydrogenation-cyclization from a relatively long lived triplet state, the reaction must proceed through the excited singlet state whose short lifetime (10^{-13} to 10^{-14} sec.)¹⁴ would necessitate a very rapid reaction which he believed would likely be of a concerted nature. As such, he ignores the possible role of oxygen.

Stegemeyer does support his further criticism with experimental data. In this, he takes exception with the excited state common to both the cis and the trans isomers by demonstrating that the phenanthrene could only be formed from an excited state reached exclusively from the cis configuration. This was achieved by performing detailed quantum yield and initial rate studies on solutions of both cis- and trans-stilbene.

For dilute solutions of the stilbene isomers ($5 \cdot 10^{-5}$ M./n-hexane) irradiated at 253.7 mμ. and 313.0 mμ. wavelengths, Stegemeyer plotted the mole fraction of phenanthrene produced (Xp), as measured by its ultraviolet absorption, versus the number of light quanta absorbed by the solution (Nq). This makes it possible to observe the initial rates of reaction starting from the two stilbene isomers. The following graph illustrates the point.



This indicates fairly clearly that the reaction proceeds from the cis form. The sudden change in rate of the trans-stilbene solution at $N_q = 6 \cdot 10^{16}$ and $313.0 \text{ m}\mu$. irradiation may be explained by the analysis of the product mixture which at this point contains 70% cis-stilbene. The distinct difference between the two wavelengths employed may be accounted for by the fact that the efficiency of isomerization is more pronounced for the longer wavelength.

These initial rates correlate quite well with the differential quantum yield observations. Here, the differential quantum yield is computed by $q_d = (N_1 \cdot V \cdot C_0 \cdot \Delta X_p) / \Delta N_q$ where N_1 is the extinguishing co-efficient, V the volume of the measuring vial (liters), C_0 the initial concentration (M/L), and X_p and N_q the changes in mole fraction and the changes in quanta absorbed by the solution, respectively. When cis-stilbene was considered, the differential quantum yield remained essentially constant with increasing N_q for both wavelengths utilized. On the other hand, trans-stilbene solutions demonstrated an increasing quantum yield, in the case of the $313.0 \text{ m}\mu$. being initially zero at the start of irradiation.

These results cast some doubt upon the original contention of a common excited state for both isomers. The relatively constant cis quantum yield indicates reaction at a constant rate throughout while the initially low quantum yield of the trans case indicates an induction period, presumably necessitated by the formation of the cis isomer. The initial rates of reaction give an identical conclusion. Hence, a reaction state proceeding from exclusively cis-stilbene seems probable.

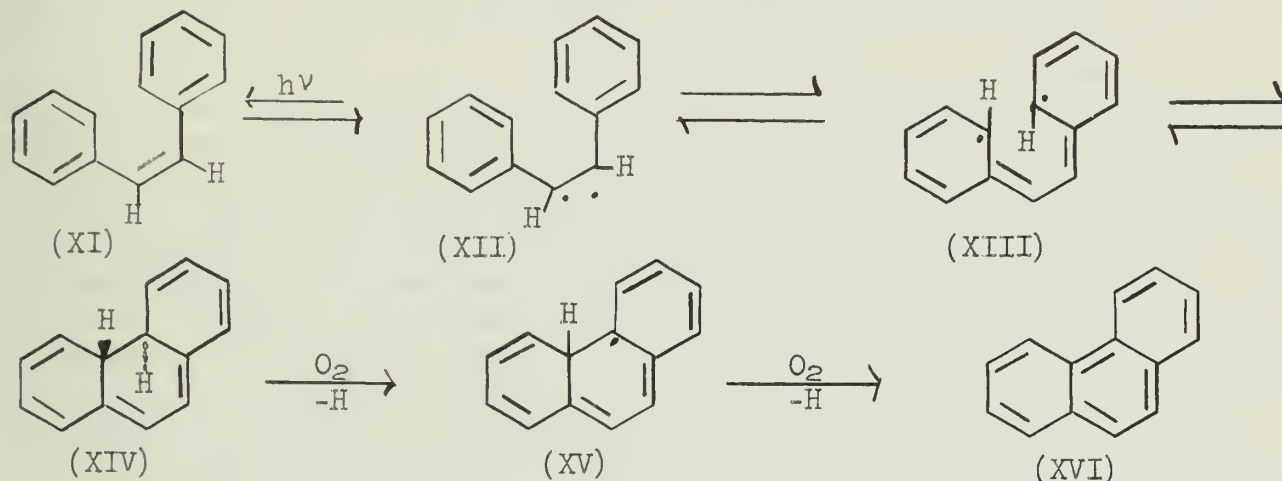
These data are subject to criticism as Srinivasan and Powers point out.¹⁰ Since Stegemeyer has ignored the oxygen dependence (below) of the reaction, irregularities in both sets of data could exist. Indeed, the slight decrease with increasing quanta absorption in both quantum yields and initial rates could well be a result of the depletion of the oxygen dissolved in the reaction media. Furthermore, Srinivasan and Powers have demonstrated an apparent concentration - quantum yield interdependence overlooked by Stegemeyer.

In a preliminary report,¹⁵ F. B. Mallory demonstrated conclusive proof of the reaction's dependence on an oxidizing agent. By performing the reaction under nitrogen after having carefully degassed the reaction solution by multiple freeze-evacuation cycles, he demonstrated no detectable phenanthrene formation in either the cis or the trans compound. He also found that molecular iodine (3 - 5 mole%) would act as a suitable hydrogen acceptor. In fact, he found that a combination of air and iodine greatly increased the synthetic utility of the reaction.

This rigorous dependence of the reaction on an oxidant has been supported by the independent work of W. M. Moore, D. D. Morgan, and F. R. Stermitz¹⁶ and by

Srinivasan and Powers.¹⁰

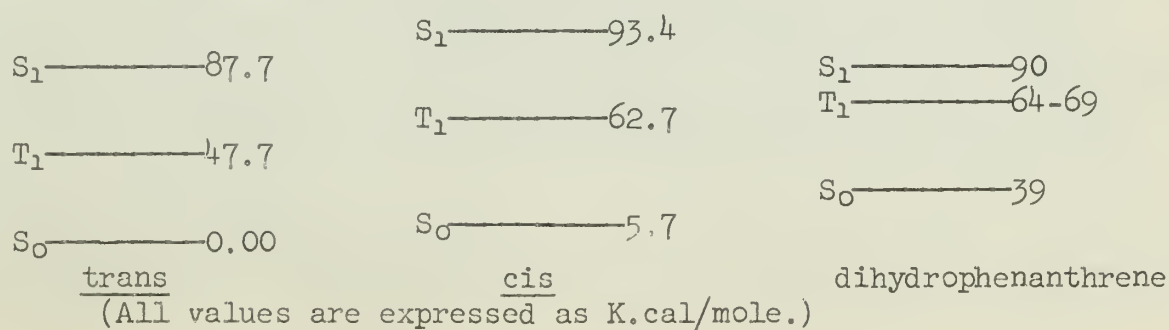
Also in this preliminary report, Mallory outlined what he believed to be the correct mechanism of the reaction. This begins with an electronically excited S_1 (XII) available to cis-stilbene (XI) exclusively. The resulting di-radical, in an alternate resonance form (XIII), cyclizes to a trans-dihydrophenanthrene intermediate (XIV) which subsequently loses hydrogen to a suitable acceptor to give phenanthrene (XVI). This final step is considered to occur in two stages, a slow proton removal to give the free radical (XV) followed by a rapid proton loss to give the observed product. This may be illustrated graphically by the following:



Mallory¹⁷ draws support for his exclusively cis precursor chiefly from Stegemeyer's original contention based on quantum yields and initial rates. These data Mallory accepts as valid. There is also support in the work of independent researchers. Moore, Morgan, and Stermitz¹⁶ irradiated dilute solutions of trans-stilbene under oxygen with a wavelength of 290-310 m μ ., where cis-stilbene has little absorption. Upon spectrophotometric analysis, the product mixture contained predominantly cis-stilbene, and negligible phenanthrene formation was observed. Hence, cyclization-dehydrogenation was apparently inhibited by denying the necessary wavelengths for excitation of the cis isomer to phenanthrene formation. The possibility that different wavelengths are necessary for phenanthrene formation from the trans isomer was not explored. A further discordant note is struck by Stegemeyer's work which utilized a wavelength of exclusively 313.0 m μ . for quite successful phenanthrene formation. Likewise, Mallory utilized the narrow wavelength range of 312.5 to 313.1 m μ . to perform extensive rate studies on the reaction of stilbene and its derivatives to form phenanthrenes.¹⁸ This experimental work must cast some doubt on the work of Moore, Morgan, and Stermitz.

Additional proof comes from the work of George S. Hammond and his students¹⁹ who observed that the yellow color of the apparent precursor to phenanthrene (see below) formed quite rapidly from irradiation of dilute cis-stilbene solutions but only gradually from irradiation of trans-stilbene solutions, presumably because the latter required an induction period in which cis-stilbene was formed by photochemical isomerization.

From Hess' Law summations utilizing data from heats of hydrogenation, heats of combustion, and various analogies, Mallory proposed the following relative energy level diagram for cis-stilbene, trans-stilbene, and the dihydrophenanthrene intermediate.



Assuming the validity of this argument, it is quite evident that the conversion of cis-stilbene T_1 to dihydrophenanthrene T_1 is an endothermic process, if the reaction were to occur with spin conservation. In addition to being energetically unfavored, the relatively long time required by such a process would not be compatible with the apparently unusually short lived cis-stilbene T_1 .¹⁴ The reaction through the S_1 excited state is given validity by Hammond's work²⁰ with photosensitizers. No cyclization was found in the irradiation of cis-stilbene solutions while utilizing such T_1 energy transfer agents as benzophenone, 9,10-anthraquinone, and benzanthrone along with excitation wavelengths which would selectively be absorbed by the sensitizer and not the substrate.

Another fact in evidence of the singlet state is the absence of quenching in the reaction. W. M. Moore, R. P. Foss and G. S. Hammond,²¹ along with many independent researchers, have found that photochemical reactions proceeding through the triplet state are markedly quenched by the presence of such paramagnetic species as molecular oxygen, the sole criteria being that the energy levels of the substrate T_1 and the quencher T_1 be of similar magnitude. Quite obviously, oxygen takes no part in quenching of this reaction. Furthermore, M. Kasha²² has found that the introduction of certain substituents into a molecule will strongly favor intersystem crossing, S_1 to T_1 state. In view of this, the inability of acetyl and nitro substituted stilbenes to cyclize to phenanthrene becomes quite significant as these substituents are known to promote such intersystem crossing.¹⁵

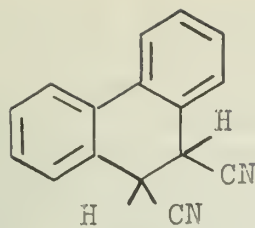
Mallory tentatively excludes the third possibility¹⁷ that cyclization could occur from an S_0 vibronically excited state, on the presumption that solvent collisional deactivation would proceed at a sufficiently rapid rate to preclude any chemical processes. Whether this can be considered valid in this case where the reaction centers are in such close proximity is a matter of conjecture at present.

In support of Schaffner's contemplated mechanism, Mallory suggests that a dihydrophenanthrene intermediate is formed upon irradiation of cis-stilbene and being unstable, is in thermal equilibrium with the starting material. Such an equilibrium, if rapid, would seem tenable in view of the 39 K.cal./mole difference between the two isomers. In the presence of a suitable oxidant, as molecular oxygen, the hydrogens at the tertiary allylic positions of the intermediate are abstracted, in preference to thermal deactivation, so as to allow phenanthrene formation.

This view receives significant experimental support from Moore, Morgan and Stermitz,¹⁶ who, upon running the reaction under a nitrogen atmosphere with a rigorously deoxygenated reaction medium, detected the formation of a yellow color (above) which gradually faded upon cessation of irradiation. The resulting reaction mixture contained no detectable quantity of phenanthrene. Exposure of this yellow solution to the atmosphere immediately following the irradiation resulted in phenanthrene formation, and careful observation of an identical reaction medium under an oxygen atmosphere afforded detection of a similar yellow color. Quantitative spectroscopic determinations revealed that the yellow color (absorption at 447 m μ .) in the presence of oxygen faded at a rate commensurate with that of the appearance of phenanthrene. This is a significant indication that the yellow color belongs to an immediate precursor of phenanthrene; it does not, however, prove that it is the dihydrophenanthrene, however likely the structure would appear, a priori. In spite of the limited nature of this information, Mallory assumes the existence of the intermediate as proposed.

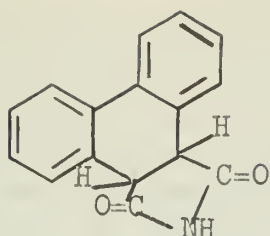
A disquieting note has been raised in the face of this line of thinking. M. W. Sargent and C. J. Timmons^{23,24} have reported the isolation of a 9,10-dihydrophenanthrene upon irradiation of both trans- α,β -dicyanostilbene and diphenylmaleinimide solutions ($CHCl_3$) under an air atmosphere. While the 9,10-dicyano-9,10-dihydrophenanthrene (XVII) was isolated in only 7% yield in this case, rigorous previous degassing and employment of an inert atmosphere gave exclusively this compound. Under air atmosphere, the 9,10-dicarboximido-9,10-dihydrophenanthrene (XVIII) occurred in a 40% yield.

These structural assignments rest primarily on spectroscopic data. In the case of the dicyano compound, the $-C\equiv N$ stretching vibration of the infrared spectrum lies well within the range of nitriles attached to aliphatic, unsaturated carbons.²⁵



(XVII)

I.R. $\text{-C}\equiv\text{N}$ 2255 cm^{-1}
 N.M.R. 5.58 τ = 2H



(XVIII)

N.M.R. 5.18 τ = 2H

Ultraviolet spectroscopic data for both compounds are quite in agreement with observations made on an authentic sample of 9,10-dihydroxy-9,10-dihydrophenanthrene. The nuclear magnetic resonance data also correlate quite well with the dihydroxy sample, each compound demonstrating a singlet of a magnitude equal to two protons in a chemical shift range of 5.18 to 5.58 τ . That

this is far downfield from the usual absorption of aliphatic, unsaturated protons²⁶ has been neither questioned nor justified. Mallory, in noting the existence of these compounds, rationalized them as arising from an alternative mode of degradation open to his dihydrophenanthrene intermediate. ~~No question is raised as to whether such a compound exists in the case of unsubstituted stilbene rearrangements.~~

The disposition of the hydrogens in the proposed dihydrophenanthrene intermediate lends itself to useful though not definitive discussion as is readily admitted. There are three considerations leading to Mallory's belief that the hydrogens are in a trans configuration. First, from models it is apparent that the transition state leading to the cis configuration leads to greater ortho-ortho¹ hydrogen steric interaction than does the trans. Whether this effect is of significant magnitude with respect to the excitation energies involved remains an open question.¹⁷

Second, a structurally analogous ring closure, that of the 2,4,6,-octatriene system,⁷ occurs to give trans-1,2-dimethyl-3,5-cyclohexane upon irradiation, and presumably the stilbene undergoes a similar rearrangement to give the trans product. The only reservation concerning this analogy is that although structurally similar, the energetic difference between product and starting material is greatly different for the two reactions. In the triene case, the product is known to be more stable than the starting material by about 16 K.cal./mole.¹⁷ On the other hand, the dihydrophenanthrene is postulated as being 39 K.cal./mole less stable than its precursor. The exact effect of this difference is difficult to assess, however.¹⁷

Finally, the formation of a cis intermediate would likely lead to formation of phenanthrene through spontaneous generation of hydrogen in a manner as that of the vapor phase reaction. This would be a reasonable assumption for the cis case in view of the 54 K.cal./mole liberated when the intermediate S_1 decomposes to the S_0 case, an energy more than enough to overcome the 49 K.cal./mole theoretically necessary. This, of course, rests on the tenuous assumption that collisional deactivation would not be such an overwhelming factor so as to give hydrogen evolution insufficiently large to be detected. This also assumes that spontaneous hydrogen elimination from the trans species would require a prohibitive molecular contortion.¹⁷

In a final note, no experimental data has been proffered to either confirm or deny Mallory's suggested¹⁵ step-wise hydrogen removal from the dihydrophenanthrene intermediate.

CONCLUSION

In spite of the numerous efforts of a large number of research groups, the photochemical rearrangement of stilbene to phenanthrene remains an unsatisfactorily characterized reaction. Several potentially powerful methods of analysis have yet to be utilized.

None of the investigators have attempted to use electron spin resonance to characterize reaction species and intermediates. Such studies could explore the possibility, hitherto unsuggested, that the yellow colored intermediate is a long lived triplet state or some other free radical state. Likewise, nuclear magnetic resonance adapted to dilute solutions could yield important information.

An unresolved problem needing further exploration is that of the cis-trans isomerization of the stilbenes. While Hammond and his research group^{19,27} have been able to show that triplet state sensitizers will activate this isomerization, spectral data¹⁴ indicate that neither the T_1 state nor the S_1 state of trans-

stilbene has sufficient mobility about the central carbon-carbon bond to allow a probable transition. This could have a direct bearing on the problem at hand.

Finally, in another area, much of the evidence upon which rests the postulation of an exclusively cis precursor is of doubtful nature. Along with repeating Stegemeyer's work under constant concentration and oxidant conditions, this point could be indisputably resolved by irradiating an equal mixture of trans-stilbene-C¹⁴ and cis-stilbene and analyzing the product mixture after low conversions. In view of the novel dihydrophenanthrenes trapped by Timmons, it would be highly instructive to label stilbene with tritium in various positions so as to positively identify the hydrogens lost in the reaction.

The above are a few points requiring further investigation; needless to say, there are surely many more. Perhaps the most certain aspect of the mechanism of this reaction is that it will undoubtedly father a good many more doctoral thesis.

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RECENT ADVANCES IN CYCLOBUTADIENE AND RELATED SYSTEMS

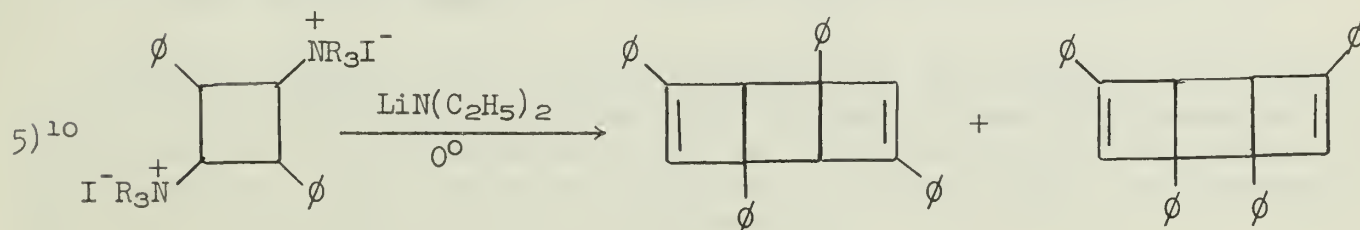
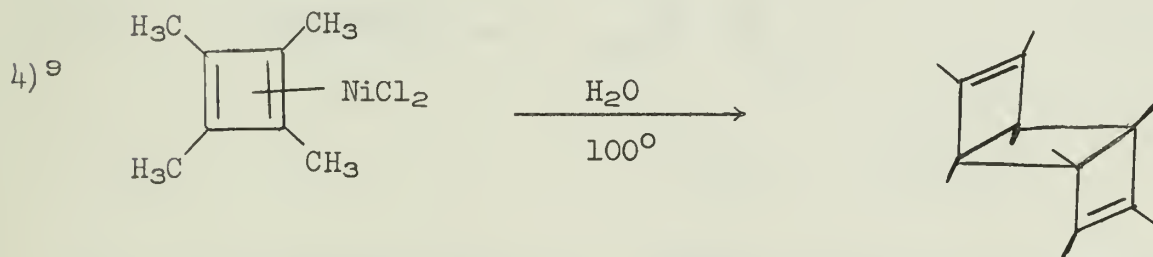
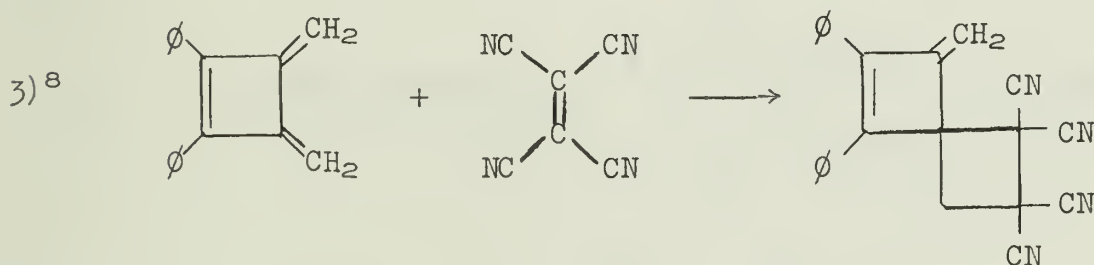
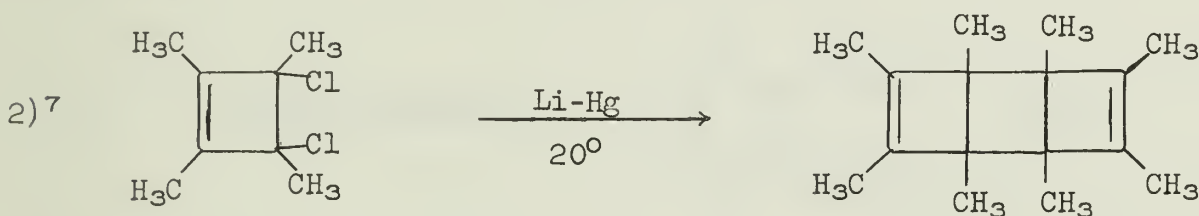
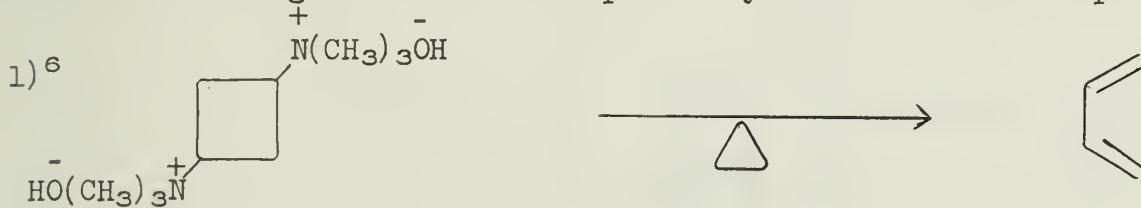
Reported by Dennis Chamot

July 16, 1965

There has been a great deal of interest among theoreticians in cyclobutadiene and compounds containing the cyclobutadiene ring system.¹ Fortunately, the theoretical predictions were advanced before much of the related experimental work was done and in fact served as a stimulus. The present availability of experimental results provides the opportunity of checking these predictions.

CYCLOBUTADIENE

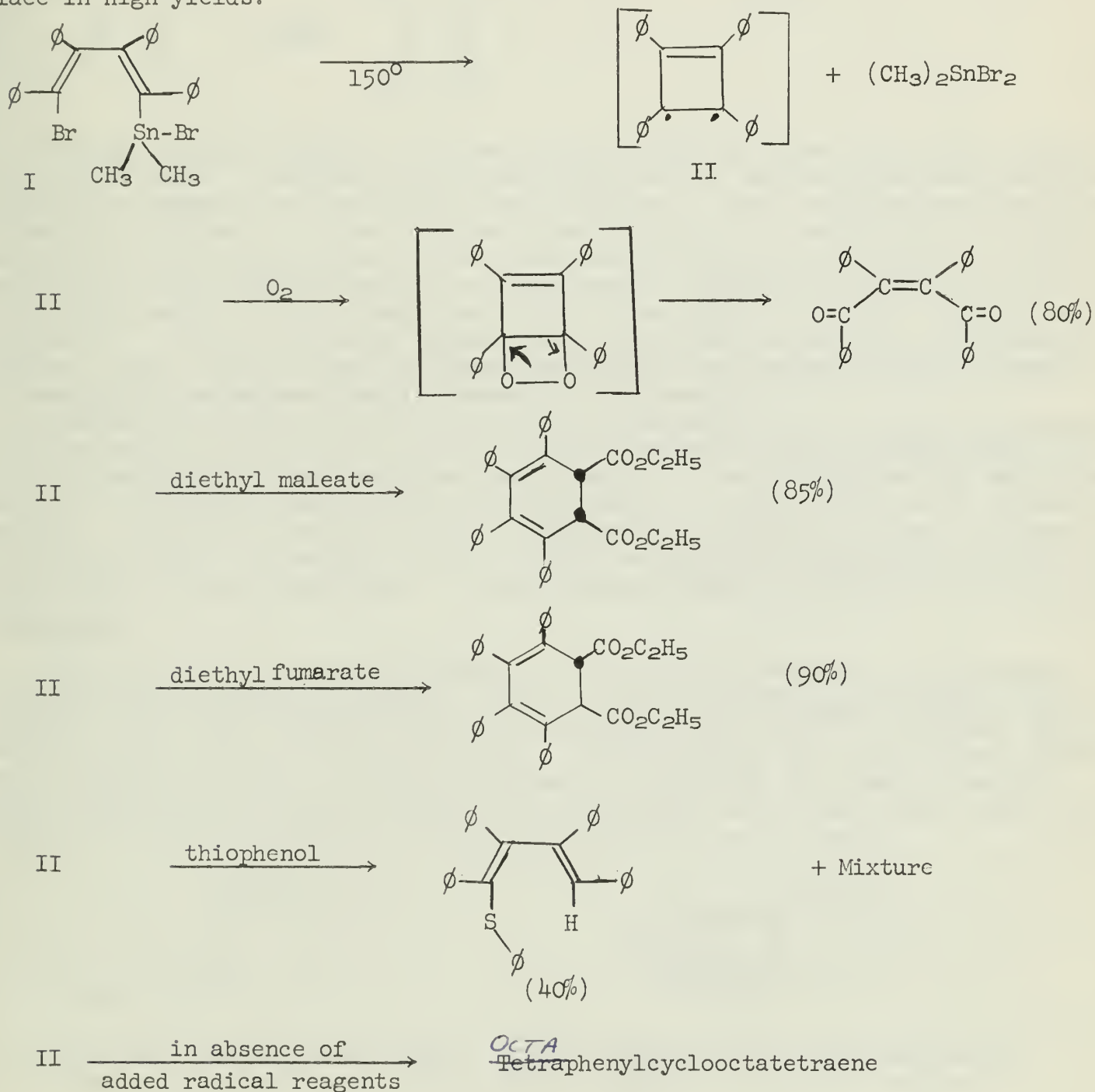
Simple molecular orbital theory indicates¹ that cyclobutadiene should be a very unstable molecule, and should exist in the triplet state. It does not fit the $(4n + 2)$ rule, and should have zero resonance energy. That the molecule is in reality highly unstable, even when substituted with alkyl or aryl groups, can easily be seen from the failure of a large number of attempts at synthesis. Some examples are outlined below:



Several workers offer evidence for the biradical nature of simple cyclobutenes. As mentioned above, Nenitzescu⁶ noted that heating cyclobutane-1,3-bis(trimethylammonium)hydroxide converted it to 1,3-butadiene. Furthermore, pyrolysis of the adduct of cyclooctatetraene and dimethyl acetylenedicarboxylate produces dimethyl

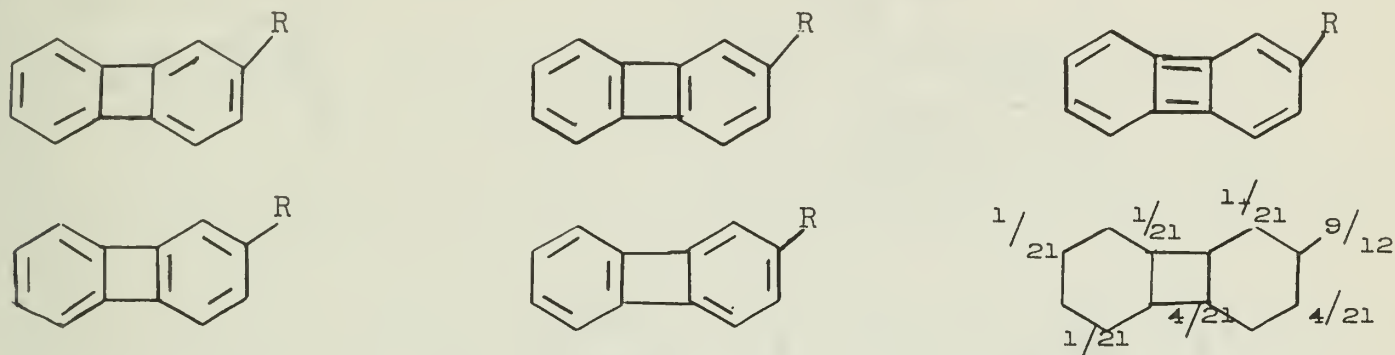
phthalate and 1,3-butadiene. In explaining these results, Nenitzescu postulated the formation of transient cyclobutadiene, which then abstracted two hydrogen atoms from neighboring molecules, with concomitant ring opening. The hydrogen abstraction reaction suggests that cyclobutadiene exists at least transiently as a triplet species.

Freedman produced tetraphenylcyclobutadiene by the elimination of dimethyltin dibromide from (4-bromo-1,2,3,4-tetraphenyl-cis,cis-1,3-butadienyl)dimethyltin bromide, I.^{11,12} The addition of the intermediate II to dienophiles and radical reagents took place in high yields.



Freedman observed that a transient green color was generated when I was decomposed. Cookson and Jones¹³ noticed the same green coloration when they generated tetraphenylcyclobutadiene through displacement from the palladium chloride complex using triphenylphosphine. The green color persisted for several hours, but disappeared immediately upon the addition of air. If the reaction is carried out in air, tetraphenylfuran is formed instead of the hydrocarbon dimer.

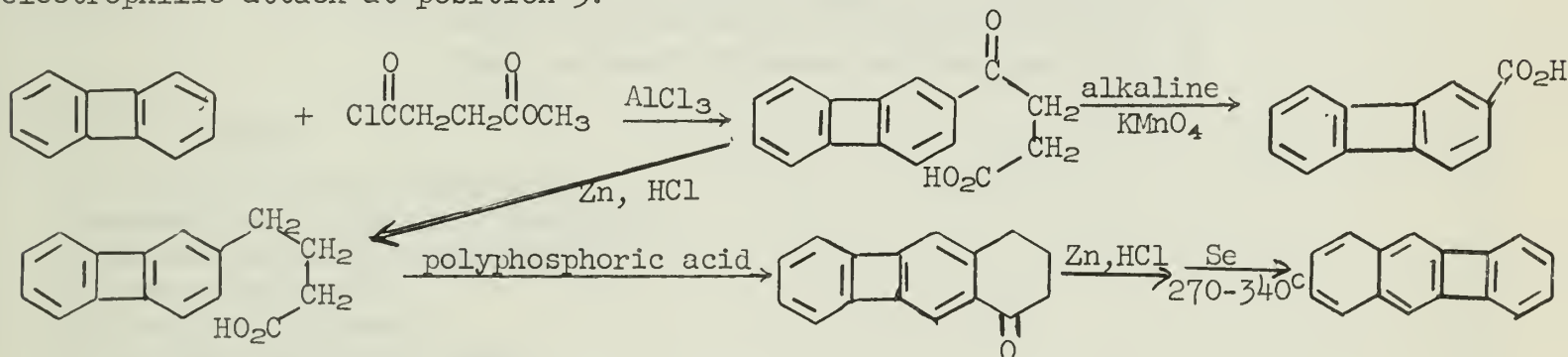
simple resonance theory. From the five resonance structures of biphenylene, it can be seen that the 1-2 and 2-3 bonds should have 3/5 and 2/5 double bond character, and so substitution should occur at position 1. However, if one calculates the extra electron density in the rings due to an electron donating group, being approximated by the isoelectronic carbanion, one finds that substitution should occur at position 3. Longuet-Higgins also suggested that this question might be resolved by studying the diazo-coupling of 2-hydroxybiphenylene.



Resonance forms of biphenylene, and calculated distribution of extra electron.

McOmie, Blatchly, and Thatte²⁹ succeeded in preparing the desired 2-hydroxybiphenylene several years later. Coupling of diazonium salts was indeed observed to occur at position 3. Bosshard and Zollinger³⁰ obtained the same result for the coupling of 2-aminobiphenylene with benzenediazonium chloride.

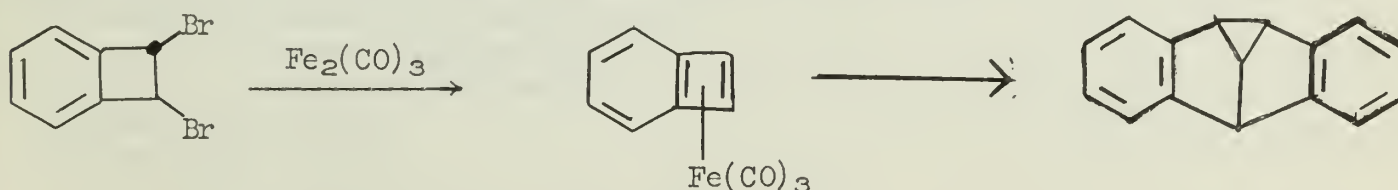
Baker, Barton, McOmie, and Searle³¹ based a synthesis of 2:3-benzobiphenylene on these theoretical predictions - namely substitution first at position 2, then electrophilic attack at position 3.



BENZOCYCLOBUTADIENE

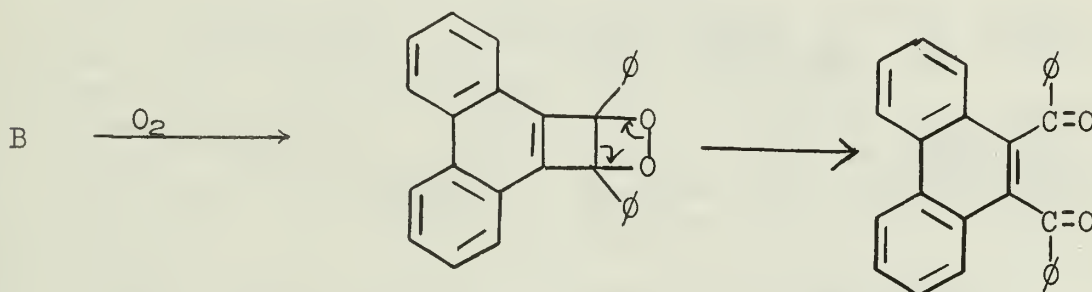
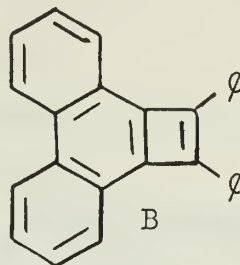
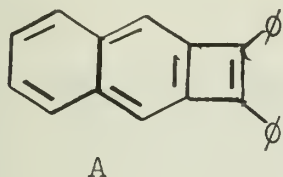
Benzocyclobutadiene should be intermediate in stability between cyclobutadiene and biphenylene. It readily dimerizes⁴ and has never been isolated. However, there have been several successful attempts at trapping benzocyclobutadiene intermediates^{4,32,33} most recently by Cava and Pohlke,³⁴ and Boulton and McOmie,³⁵ who used 1,3-diphenylisobenzofuran and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene, respectively, as trapping agents.

Pettit was able to isolate the iron-tricarbonyl complex of benzocyclobutadiene.¹⁹ Attempts to generate the free hydrocarbon led to a dimeric product whose structure was assigned on the basis of n.m.r. and molecular weight data.



The first monomeric benzocyclobutadiene to be isolated was 1,2-diphenylnaphtho[b]cyclobutadiene,³⁶ prepared by Cava, Hwang, and Van Meter. The authors argue that the stability of A (see below) could be attributed not only to the resonance and steric effects of the two phenyl rings, but also to the fact that the cyclobutadiene ring was fused to a position of low π -bond order. They further suggest that the fusion

of the cyclobutadiene ring to a position of high π -bond order, such as the 9-10 bond of phenanthrene, would result in a molecule of much lower stability. This appears to be the case. Attempts³⁷ to synthesize B by the same method³⁶ used for A did not lead to the desired product; but to 9,10-dibenzoylphenanthrene, which may arise from oxygen addition to B, followed by rearrangement.



APPENDIX

New Stable Biphenylenes and Benzocyclobutenes

(For compounds prepared earlier, see ref. 4)

<u>Name</u>	<u>Ref.</u>
2-Acetamido-3-bromobiphenylene	38
2-Acetamido-3-phenylazobiphenylene	30
2-Amino-3-phenylazobiphenylene	30
2,3-Benzobiphenylene	31*
Biphenylene-2-aldehyde	39
β -2-Biphenyleneacrylic acid	39
4-Bromo-1,2,3,6,7,8-hexamethoxybiphenylene	40
2- β -Carbomethoxypropionylbiphenylene	31
2- β -Carboxypropionylbiphenylene	31
2-3'-Carboxypropylbiphenylene	31
2,3:6,7-Dibenzobiphenylene	41*
5,6-Dibromobenzo[a]biphenylene	33
2,3-Dimethoxybiphenylene	29
2,7-Dimethoxybiphenylene	42
2,7-Dimethoxy-1,3,6,8-tetramethylbiphenylene	42
3,6(7)-dimethyl-1,8(5)-dinitrobiphenylene	47
1,4-Diphenyl-2:3-benzobiphenylene	43
1,2-Diphenylnaphtho[b]cyclobutadiene	36
1,2,3,6,7,8-Hexamethoxybiphenylene	42
1,2,4,5,7,8-Hexamethoxybiphenylene	44
2-Hydroxybiphenylene	29
Octamethoxybiphenylene	44
1,4,5,8-Tetraacetoxy-2,3:6,7-dibenzobiphenylene	46
3',4',5',6'-Tetrahydro-2,3-benzobiphenylene	31
3',4',5',6'-Tetrahydro-3'-oxo-2,3-benzobiphenylene	31
1,4,5,8-Tetrahydroxy-2,3:6,7-dibenzobiphenylene	46
2,3,6,7-Tetramethoxybiphenylene	42
1,4,5,8-Tetramethoxy-2,3:6,7-dibenzobiphenylene	46

1,2,3,8-Tetramethoxy-6,7-dihydrobiphenylene	40
1,2,7,8-Tetramethoxy-4,5-dimethylbiphenylene	44
1,4,5,8-Tetraphenyl-2,3:6,7-dibenzobiphenylene	45

* = new synthesis of known compound

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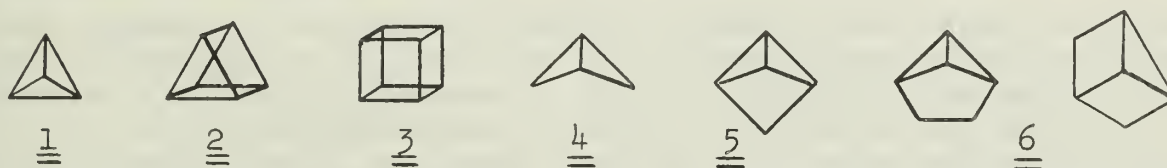
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SYNTHETIC APPROACHES TO THE ZERO-CARBON BRIDGE IN STRAINED POLYCYCLIC SYSTEMS

Reported by Roger A. Smith

July 19, 1965

Interest in the synthesis and chemistry of small polycyclic hydrocarbons has become intense. These highly fused molecules, the more famous of which are tetrahedrane 1, prismane 2, and cubane 3, at once challenge synthetic prowess and promise structural insight. The recent synthesis of bicyclobutyl 4, tricyclopentyl 5, and tricyclohexyl systems 6 has already contributed greatly to the understanding of bonding and reactivity in strained ring compounds. The synthetic realization of cubane has encouraged the pursuit of molecules such as 1 and 2, and has provided molecular orbital theory and spectroscopy with a nominally complex (i.e. eight carbon atoms) but symmetrically simple hydrocarbon against which to test their mettle. That present interest in systems such as these is both high and widespread attests to their chemical importance.



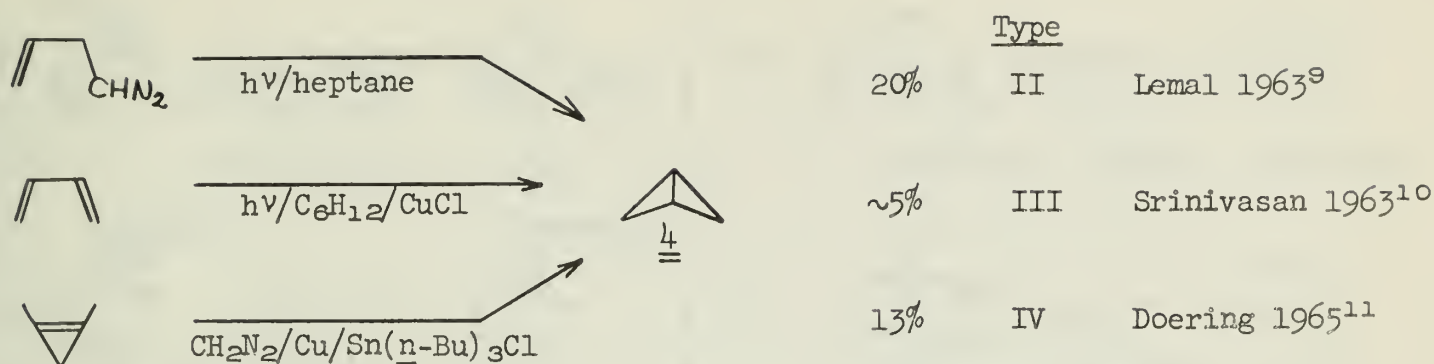
One of the most fruitful aspects of current research on the chemistry of strained polycyclic molecules is the use of carbon-13 n.m.r. to determine C-H acidities. The equation of Muller and Pritchard,¹ which correlates C¹³H coupling constants with the extent of s-character in the C-H bond, has provided much insight into orbital hybridization in highly strained carbocycles.^{2,3,4} Hybridization and reactivity, however, are not the subject of this report. Neither are several other intriguing features of the chemistry of these systems.^{5,6} While theoretical considerations understandably capture much of the interest in strained polycyclic hydrocarbons, a good deal would seem to be gained by an ordered presentation of the many systems now accessible, together with their synthesis. This seminar attempts such a review.

Characteristic of all the syntheses to be presented is the introduction of at least one new zero-carbon bridge. "Zero-carbon bridge" is intended to signify a bond between two carbon atoms the formation of which increases the degree of ring fusion in the system. Synthetic approaches may be conveniently grouped into four main reaction types: (I) transannular eliminations, (II) intramolecular carbene reactions, (III) photoisomerizations, and (IV) cycloadditions. A fifth group is made necessary by the presence of several miscellaneous cases. Where mechanism remains in doubt, the reaction will be classified on a tentative basis. Since it would far exceed the scope of a seminar such as this to thoroughly cover the large number of examples in the recent literature, a survey of representative synthetic approaches to the systems of interest must here suffice. In most instances the references lead to work not explicitly presented. Before discussing each of the groups in turn, it may be informative to consider synthetic routes to the simplest strained polycyclic hydrocarbon, bicyclo [1.1.0] butane, 4.

The first compound with a bicyclobutane structure, 1-carbomethoxybicyclobutane, was reported in 1959 by Wiberg.⁷ Since then the parent compound 4 has been synthesized, and simple derivatives made by reactions from each of the four main types (Figure 1).

Figure 1
Bicyclo[1.1.0]butane synthesis.

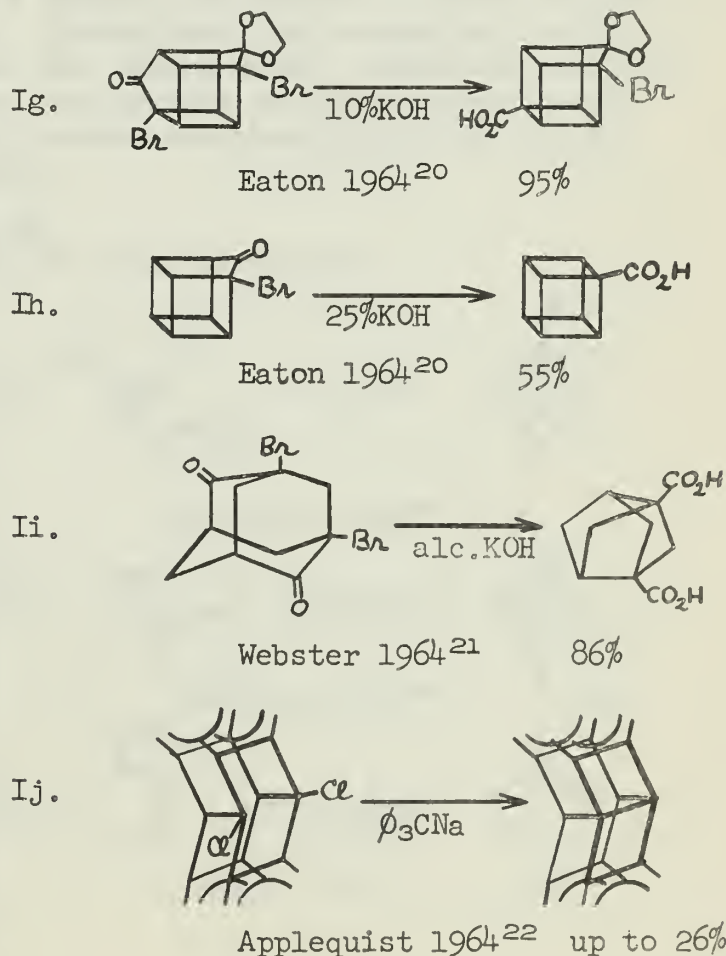
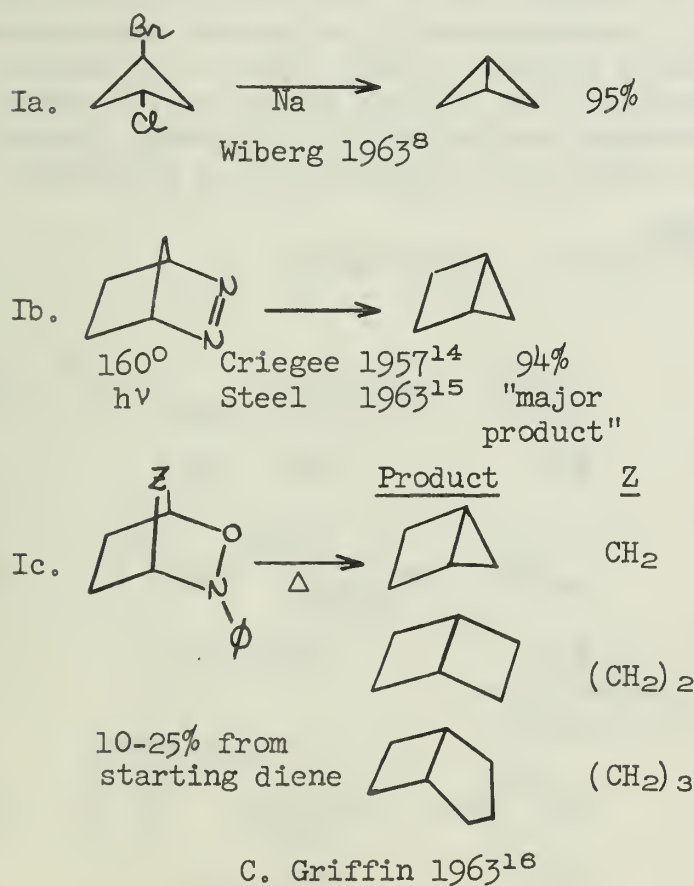


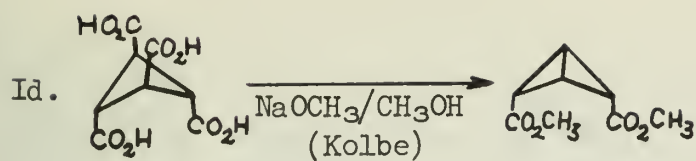


(I) TRANSANNULAR ELIMINATIONS

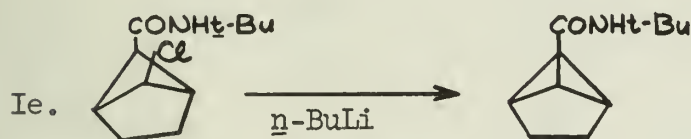
In this approach a zero-carbon bridge is formed by the thermal or photolytic transannular elimination of N_2 , CO ,¹² or ONO , by elimination of HX with strong base, by elimination of X_2 with alkali metals, or by electrolytic elimination of CO_2 (Kolbe). It is also probably easiest to regard reactions of the Favorskii type as transannular eliminations in the formal sense in view of the mechanistic uncertainties which have arisen.¹³ Although this approach leads to only one bridge, and the precursors frequently require specific functionality, the position of the new bridge is more predictable than in some of the other reaction types. Representative examples of type I appear in Table I.

Table I
Systems achieved by transannular elimination.

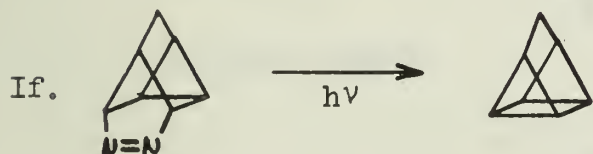




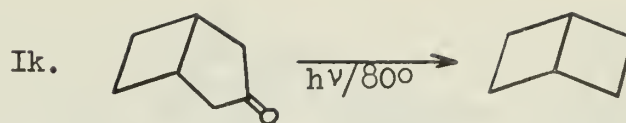
G. Griffin 1965¹⁷ ~15%



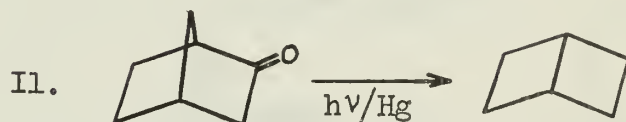
Meinwald 1963¹⁸



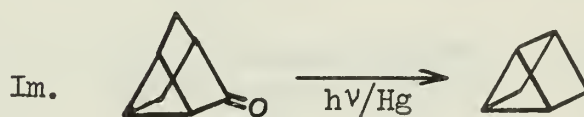
Moriarty 1963¹⁹ 35%



Srinivasan 1960²³ "low yield"



Srinivasan 1961²⁴



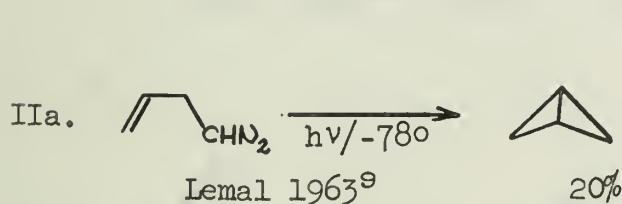
Lemal 1964²⁵ ~5%

(II) INTRAMOLECULAR CARBENE REACTIONS

There are two intramolecular paths to zero-bridges which may be followed by a carbene, C-H insertion and C=C addition. The latter, introduced by Stork in 1961,²⁶ has been used most often, and appears to be a dependable route to strained tricyclic structures containing a three-membered ring. Furthermore the concomitant introduction of a second bridge, usually of one or two carbon atoms, both increases the fusion of the system and, if an α -diazoketone (accessible by the standard Arndt-Eistert synthesis) is the carbene precursor, creates the possibility of carbonyl elimination to form another zero-carbon bridge.

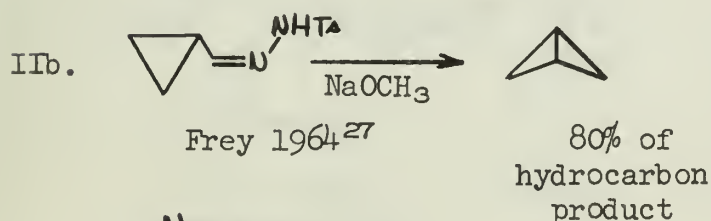
Table II

Intramolecular carbene routes to strained systems.



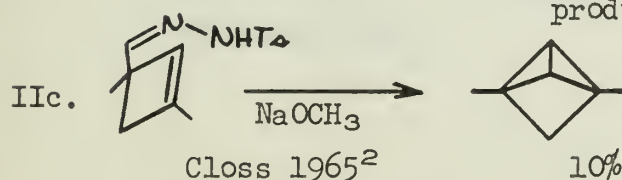
Lemal 1963⁹

20%



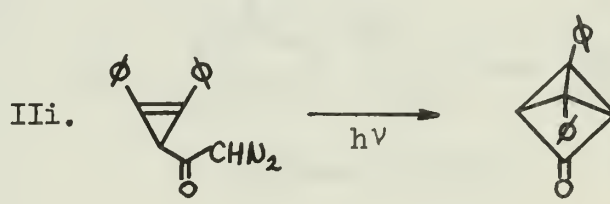
Frey 1964²⁷

80% of hydrocarbon product

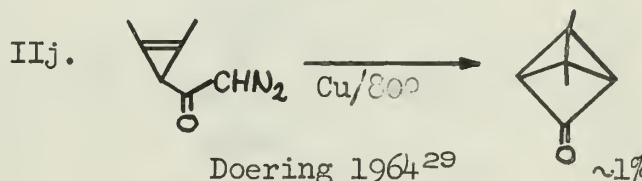


Closs 1965²

10%

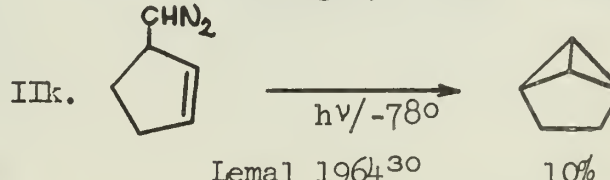


Masamune 1964²⁸



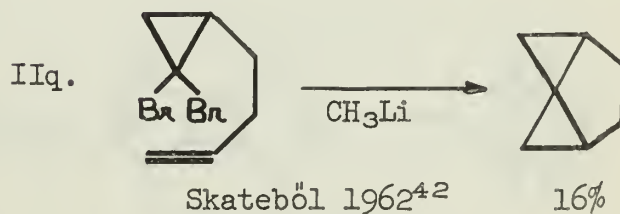
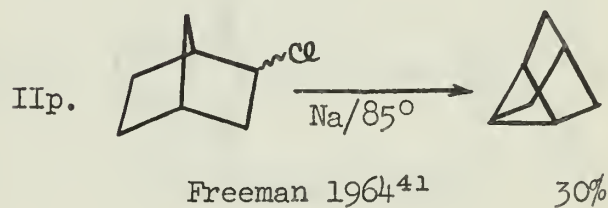
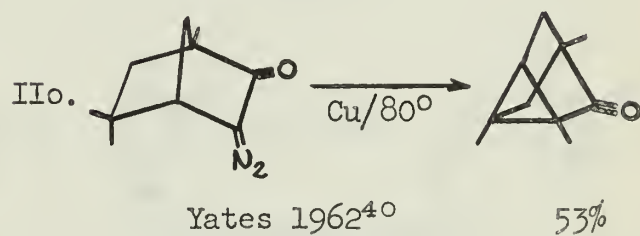
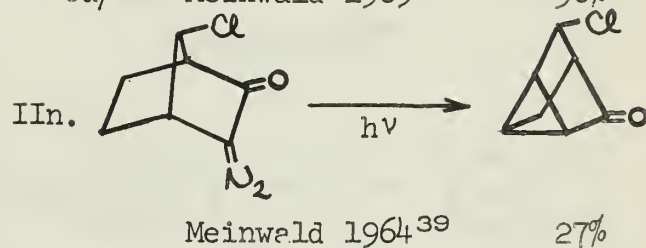
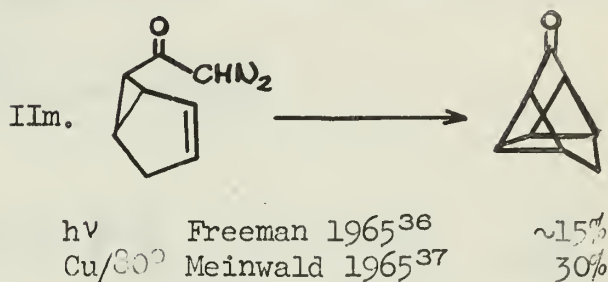
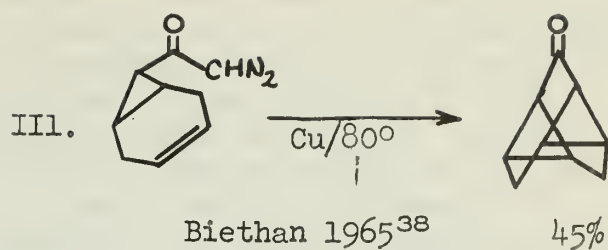
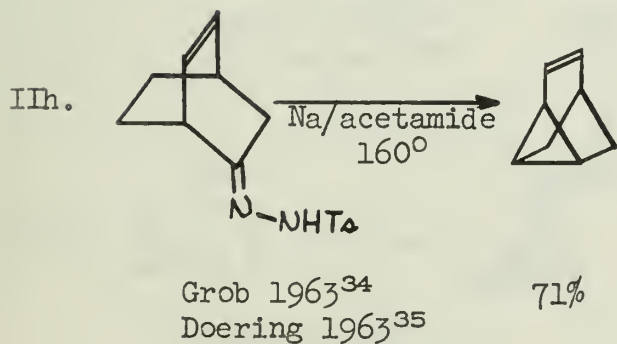
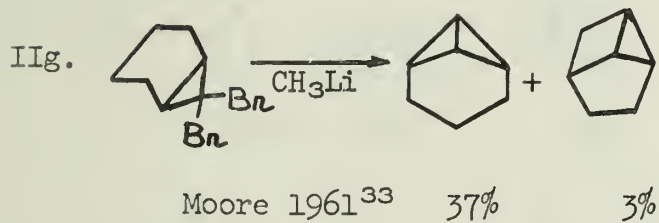
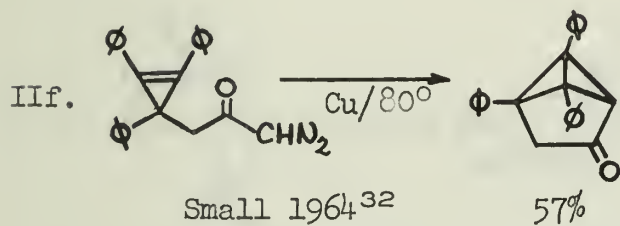
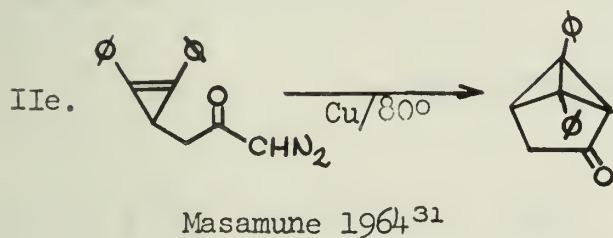
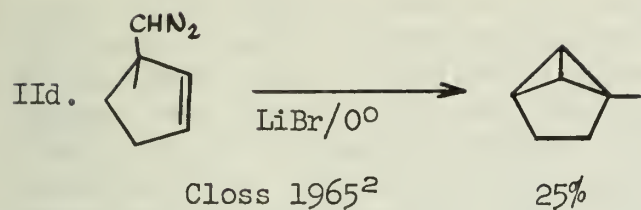
Doering 1964²⁹

~1%



Lemal 1964³⁰

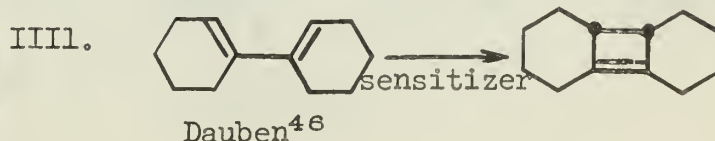
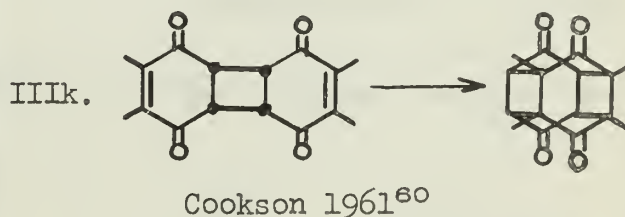
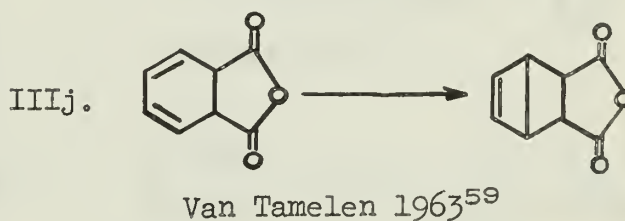
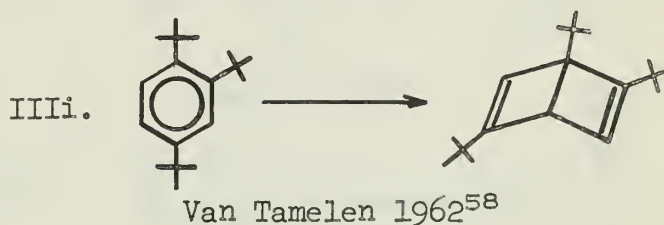
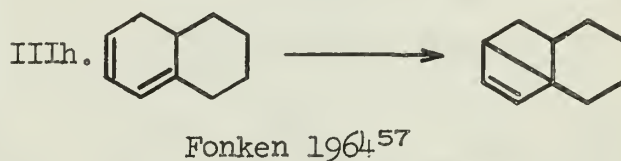
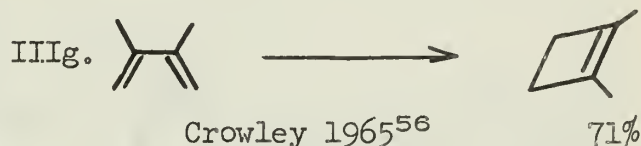
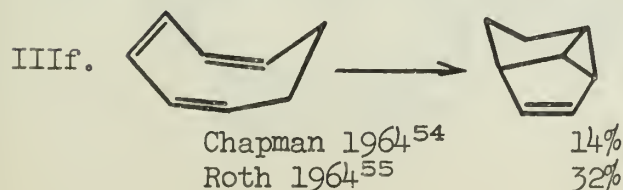
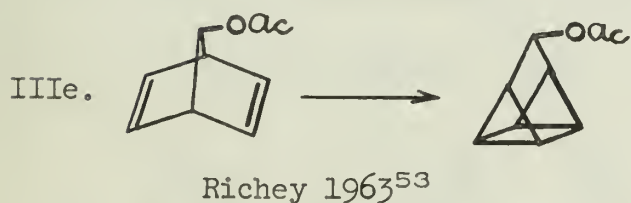
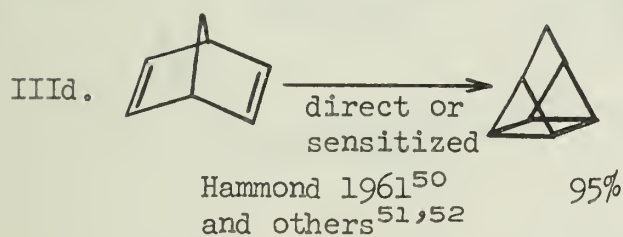
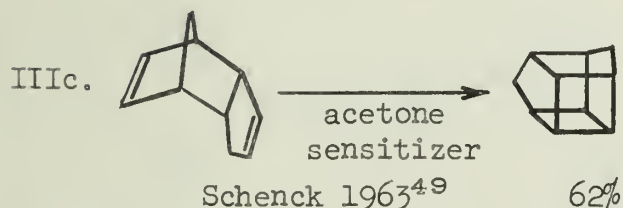
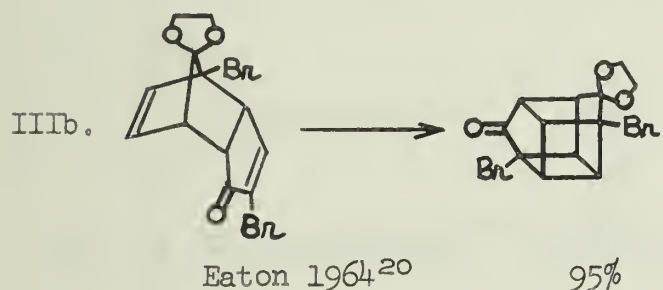
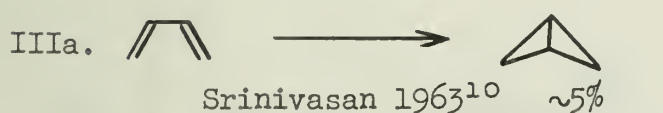
10%



(III) PHOTOISOMERIZATION⁴³

The irradiation of dienes and trienes provides in many cases a simple (if not always predictable) route to the simultaneous formation of two zero-carbon bridges. The use of organic photosensitizers has greatly extended the horizon of synthetic photochemistry.⁴⁴ Photoisomerization of certain Diels-Alder adducts,⁴⁵ cyclic dienes, and linear 1,3-dienes has afforded highly strained structures, not infrequently from readily available starting materials. Isomerization of 1,3-cyclohexadienes has led to cyclobutene structures in a wide range of systems.⁴⁶ Reactions of the type IIIc (Table III) are essential steps in the syntheses of the pentacyclic "cage" molecules,^{47,48} such as cubane.²⁰

Table III
Photoisomerization to strained systems.

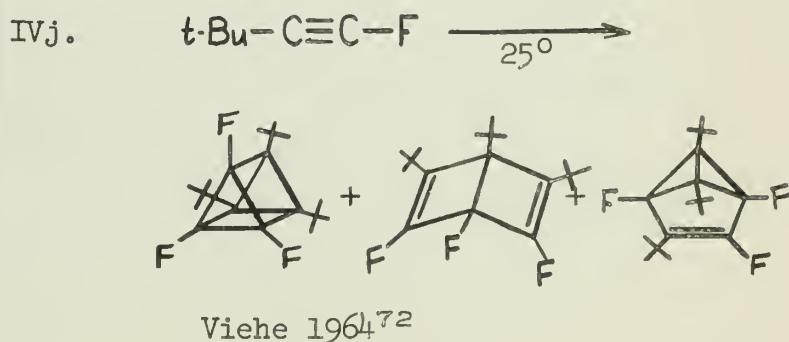
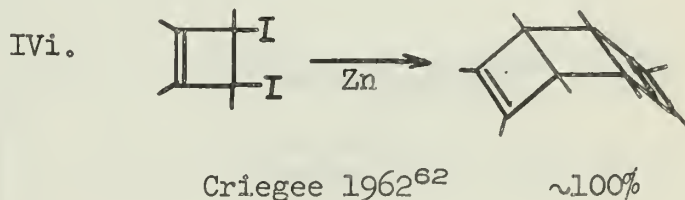
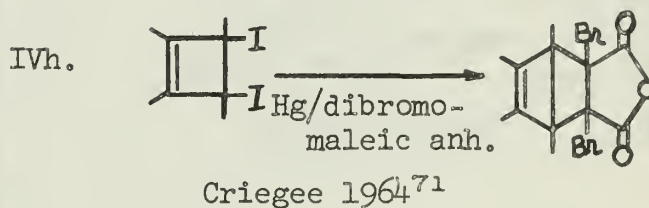
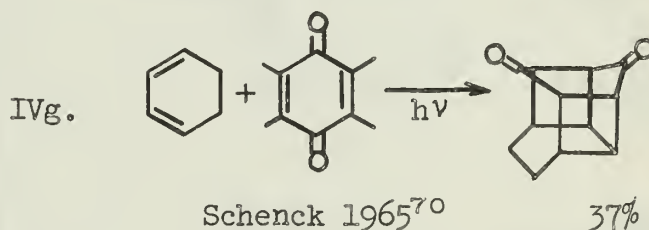
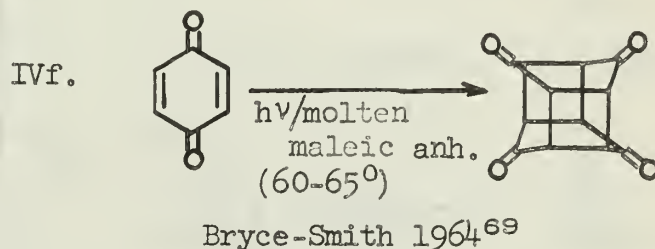
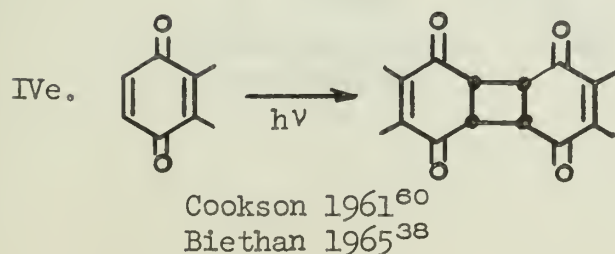
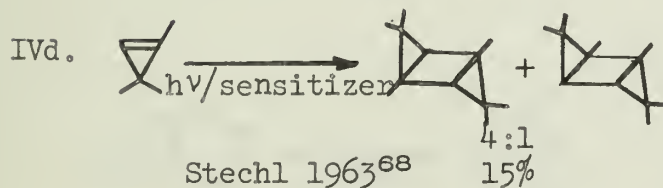
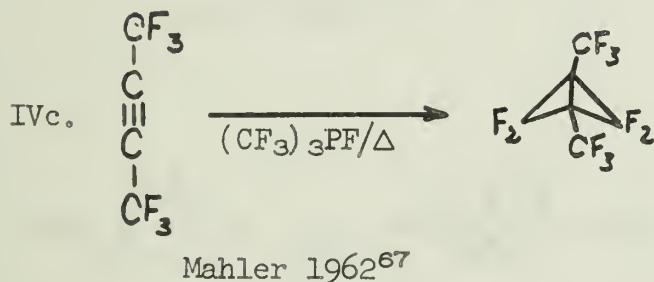
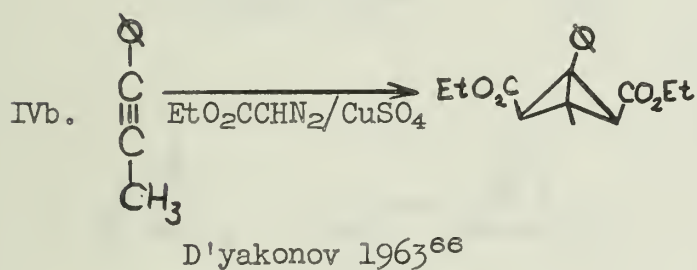
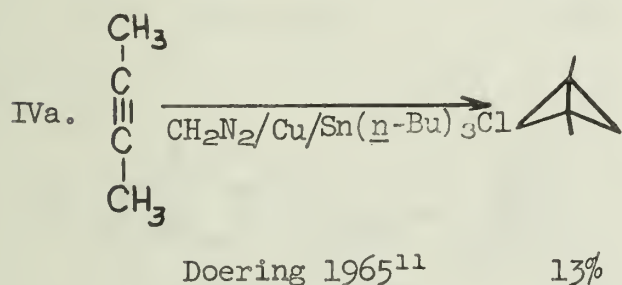


(IV) CYCLOADDITIONS

Though limited for the most part to dimerizations, trimerizations, methylene addition to acetylenes, and a few reactions akin to IVg (Table IV), this approach offers an interesting variety of strained polycyclic molecules from relatively simple precursors. Thermal 2+2 cycloadditions,⁶¹ and reactions thought to be cyclobutadiene dimerizations^{62,63,64} have been presented elsewhere, and are restricted to the formation of cyclobutanes and cyclobutenes. The dimerizations of *p*-quinones and cyclopentadieneones,³⁸ and norbornene and norbornadiene⁶⁵ have offered straightforward routes to cage molecules. The examples listed in Table IV represent cycloaddition routes to zero-carbon bridge formation.

Table IV

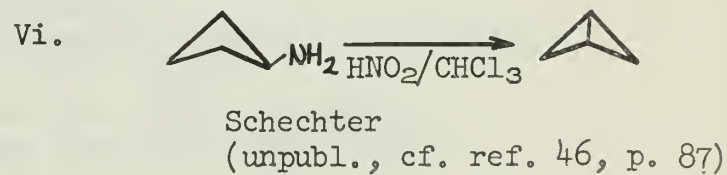
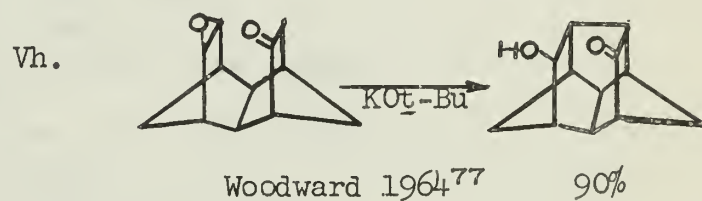
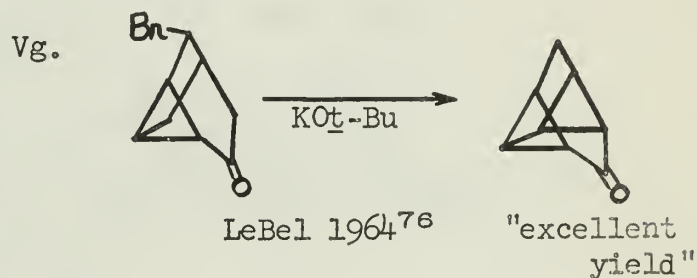
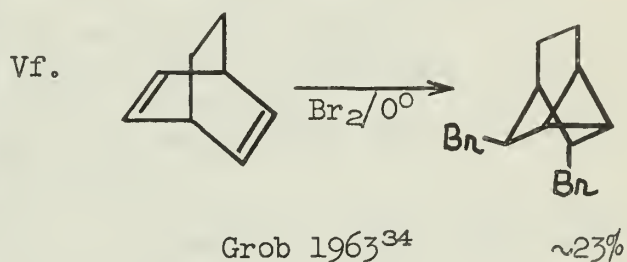
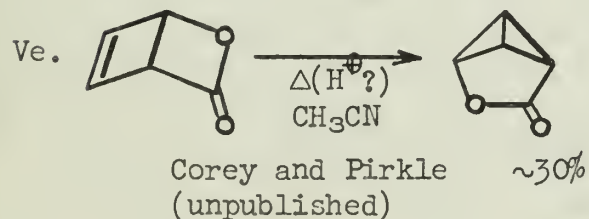
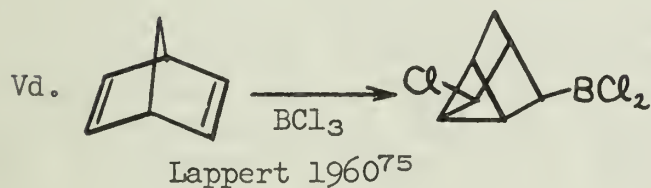
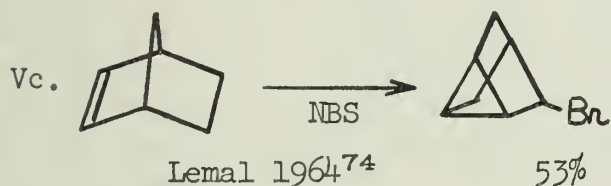
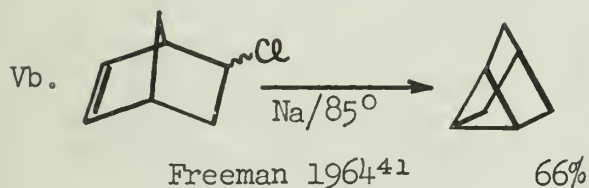
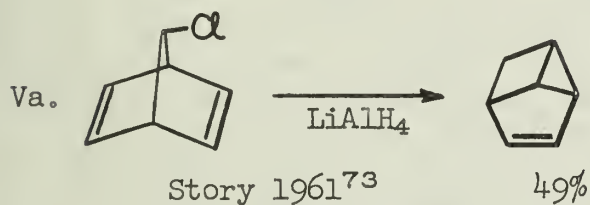
Cycloaddition routes to strained structures.



(V) MISCELLANEOUS REACTIONS

If the reactions of this group tend to lack breadth of scope, they do offer more or less unique routes to strained compounds, often leading to functionality of a different kind from that resulting in reactions of the four main approaches to zero-carbon bridges.

Table V
Miscellaneous routes to zero-carbon bridges.



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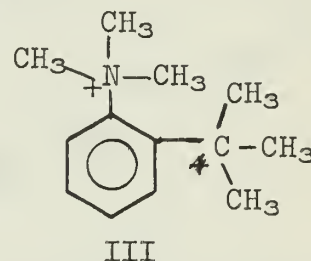
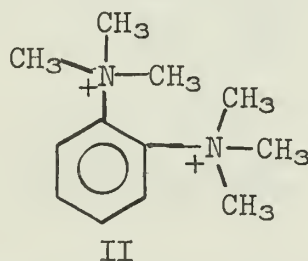
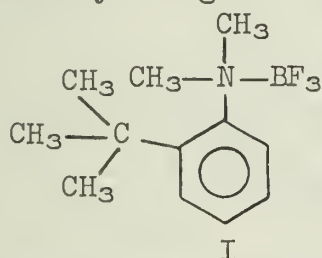
ORTHO-DI-t-BUTYLBENZENES

Reported by Mildred McDaniel

July 21, 1965

INTRODUCTION

In 1953, H.C. Brown and co-workers¹ published a series of papers on the amount of energy required to form certain strained compounds, including o-di-t-butylbenzene. Instead of attempting to prepare o-di-t-butylbenzene, they chose to attempt the preparation of "homomorphs" or molecules with similar molecular dimensions. Boron trifluoride failed to add to o-t-butyl-N,N-dimethylaniline in an attempt to prepare I. The heat of reaction of boron trifluoride with o-t-butyl-N,N-dimethylaniline was estimated to be 25 kcal/mole. In view of the failure of the reaction to proceed the strain in the "homomorphs" of o-di-t-butylbenzene were estimated to be of at least that magnitude. Brown and Nelson² also heated o-phenyldiamine and o-t-butyl-N,N-dimethylaniline with methyl iodide in an attempt to prepare II and III respectively. Negative results were also obtained in this case.

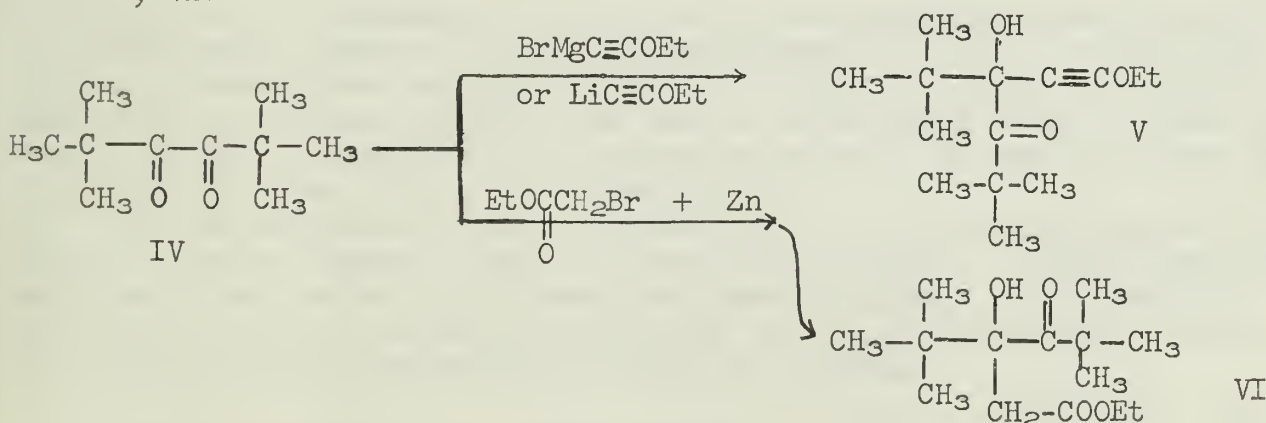


These attempts to prepare "homomorphs" led Brown to state that the synthesis of o-di-t-butylbenzene "will probably require reactions of unusually high driving force and the avoidance of conditions conducive to molecular rearrangement and isomerization."³

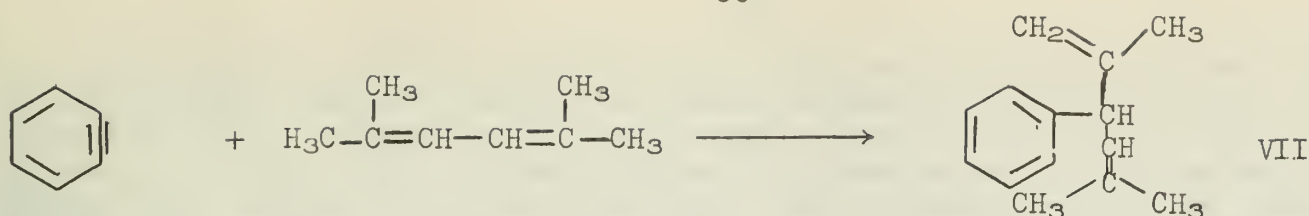
In this abstract several of the methods used to prepare o-di-t-butylbenzene and its derivatives are described, and the current work on the chemistry of these compounds is surveyed.

SYNTHESIS

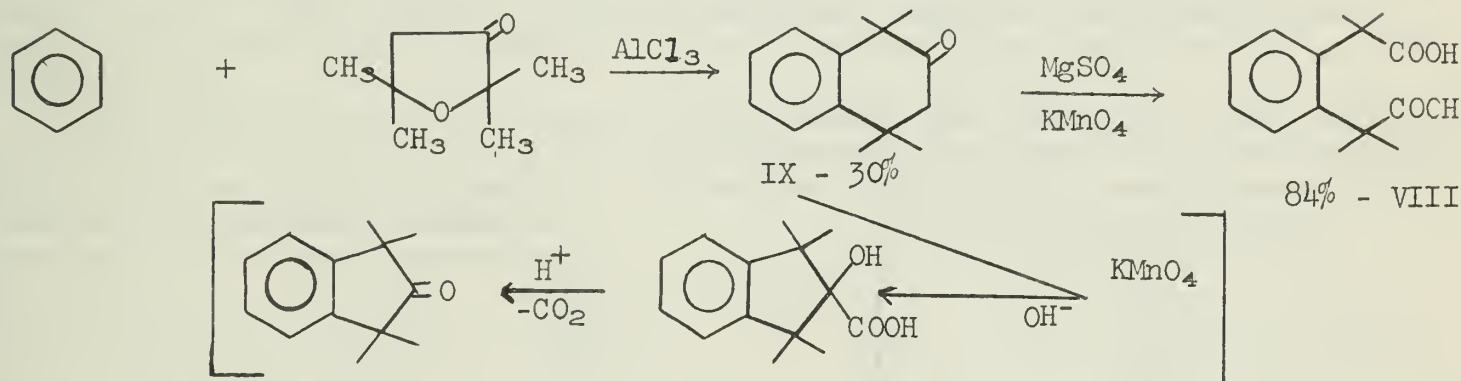
After Brown's work, Newman and Kahle⁴ tried to prepare intermediates for the conversion into o-di-t-butylbenzene by treating dipivaloyl (IV) with ethoxyethynylmagnesium bromide, ethoxyethynyllithium and ethylbromoacetate and zinc. For the ethoxyethynyl reactions the only condensation product was V and for the ethylbromoacetate, VI.



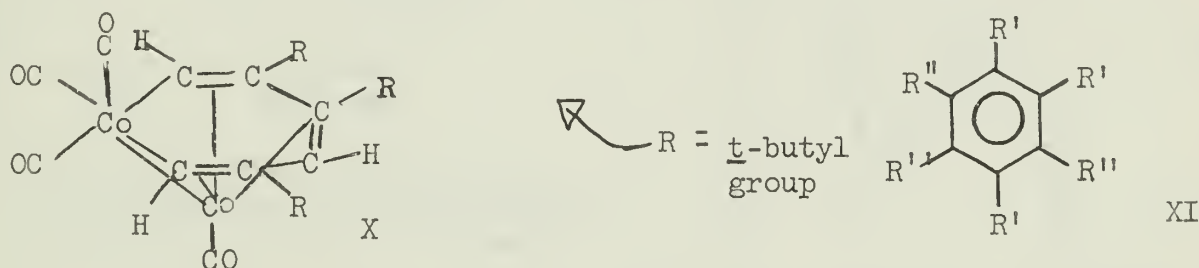
E. M. Arnett⁵ also tried to synthesize o-di-t-butylbenzene through a Diels-Alder condensation of benzyne with 2,5-dimethyl-2,4-hexadiene. No 1,1,4,4-tetramethylnaphthalene (which presumably could be oxidized to the benzene derivative) was formed. The n.m.r. spectrum of the product showed a 3:5:10 ratio of ethylenic:aromatic:aliphatic protons, suggesting that VII was produced in the condensation.



Bruson, Grant and Bobko⁶ were the first to achieve the synthesis of a derivative of *o*-di-*t*-butylbenzene, namely *o*-phenylenediisobutyric acid (VIII). Using a Friedel-Crafts condensation of benzene and 2,2,5,5-tetramethyltetrahydrofuranone, Bruson and coworkers made 1,1,4,4-tetramethyltetralone (IX). On a permanganate oxidation in the presence of magnesium sulfate, this tetralone gave VIII. The magnesium sulfate prevented development of a strongly basic condition. The observed melting point of the *o*-phenylenediisobutyric acid was 181-183°.

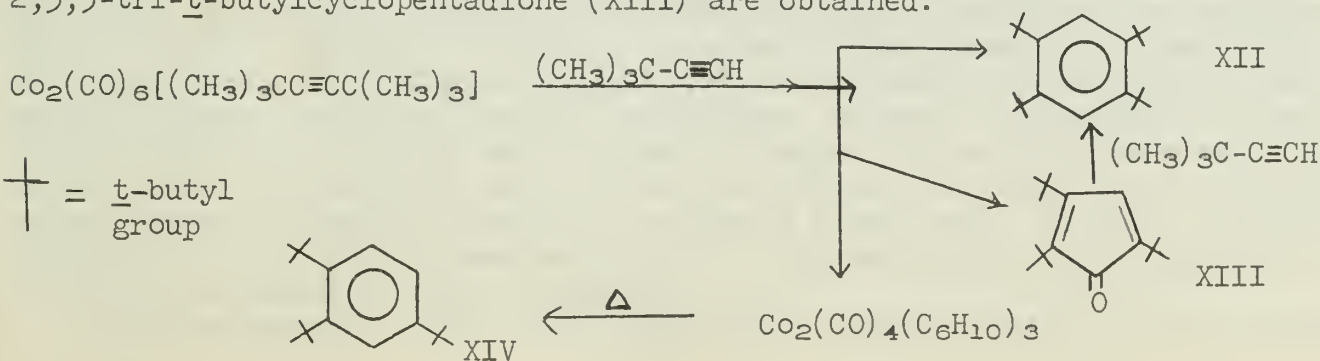


Next an *o*-*t*-butylbenzene compound was prepared by Krüerke, Hoogzand and Hübel.^{7,8} They made the cobalt complex, $\text{Co}_2(\text{CO})_4[(\text{CH}_3)_3\text{CC}_2\text{H}]_3$ which gave 1,2,4-tri-*t*-butylbenzene (XIV) upon the slow addition of bromine or upon heating. They assigned a possible structure X to the complex. The aromatic substitution pattern was invariably unsymmetrical (XI) regardless of the alkyne used in the cobalt complex.⁹



The heat of combustion for 1,2,4-tri-*t*-butylbenzene showed a higher value (2657.5 ± 0.8 kcal/mole) than for 1,3,5-tri-*t*-butylbenzene (2640 ± 0.9 kcal/mole). The difference between these energies, 16.8 ± 1.7 , could be called the strain energy of 1,2,4-tri-*t*-butylbenzene and differs from the estimated value of H.C. Brown³ by about 8.2 kcal. By way of comparison the difference in heats of combustion for *cis* and *trans*-di-*t*-butylethylene is 10.5 ± 0.5 kcal/mole.¹⁰

Hoogzand and Hübel¹¹ later prepared 1,2,4,5-tetra-*t*-butylbenzene using a cobalt carbonyl complex synthesis and an alternative synthesis. When $\text{Co}_2(\text{CO})_6[(\text{CH}_3)_3\text{CC}_2\text{C}(\text{CH}_3)_3]$ is heated under reflux with *t*-butylacetylene in ligroin for 60 hours, an 11% yield of 1,2,4,5-tetra-*t*-butylbenzene (XII) and approximately the same yield of 2,3,5-tri-*t*-butylcyclopentadione (XIII) are obtained.



The compound, 1,2,4-tri-t-butylbenzene (XIV) was eluted in the same ligroin chromatographic fraction with XII in a yield of about twice that of XII. The cyclopentadione (XIII) appeared in the benzene-methylene chloride chromatographic fraction in about 10% yield. The compound XIII can be converted to 1,2,4,5-tetra-t-butylbenzene upon heating with t-butylacetylene. This reaction is cited as proof that XIII has the assigned structure along with elemental analysis and an infrared spectrum showing a band at 5.83μ due to the carbonyl group.

The structure of 1,2,4,5-tetra-t-butylbenzene was assigned on the basis of the n.m.r. spectrum. In carbon disulfide the spectrum shows only two peaks. The peaks lie at $\tau = 2.46$ ppm and at $\tau = 8.52$ ppm relative to tetramethylsilane (TMS), with an area ratio of 2:34.5 respectively. The expected area ratio is 2:36 for the aromatic to aliphatic protons.

Almost simultaneously Arnett and coworkers¹² prepared a tetra-t-butylbenzene using the same cobalt complex and t-butylacetylene. With the same spectra data as Hoogzand and Hübel, Arnett suggested that the correct compound might be 1,2,4,5-tetra-t-butylbenzene.

The ultraviolet spectra of these t-butylbenzenes show distinctive characteristics. In comparison to the other alkyl-substituted benzenes, the spectra of these compounds in the region of 260-280 $m\mu$ exhibit a bathochromic shift with a loss of aromatic fine structure and decreased intensity

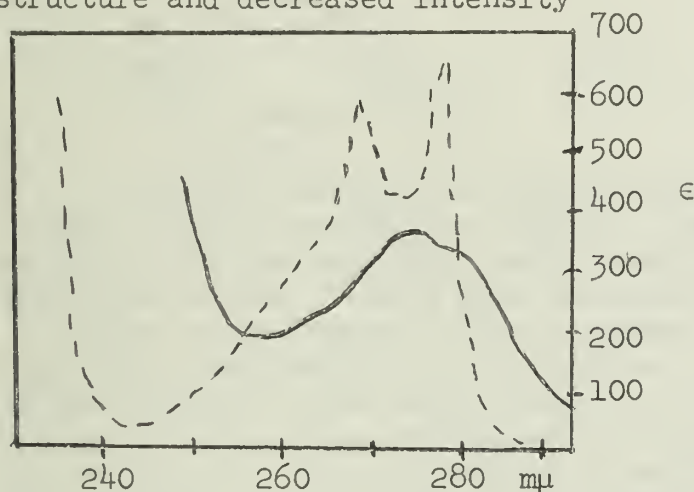


Fig. 1:¹¹ — 1,2,4,5-tetra-t-butylbenzene
-- 1,2,4,5-tetra-iso-propylbenzene
ultraviolet spectrum in n-hexane

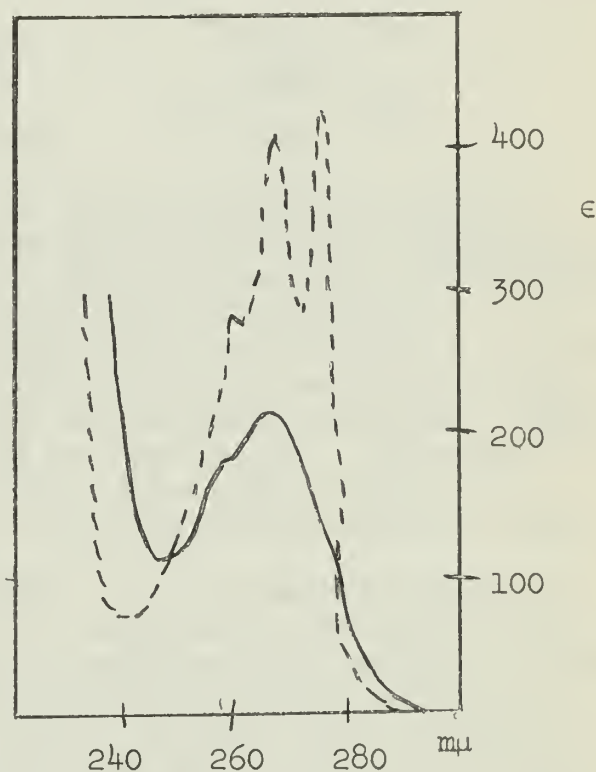
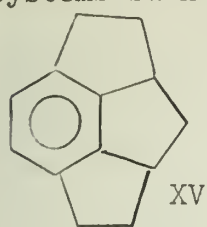


Fig. 2:¹³ — 1,2,4-tri-t-butylbenzene
-- 1,2,4-tri-iso-propylbenzene
ultraviolet spectrum in n-hexane

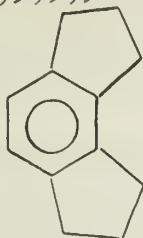
Dale¹³ compared the ultraviolet spectra of 1,2,4-alkylbenzenes and found that anomalous spectra were obtained only when the alkyl substituent was a t-butyl group. (Fig. 2) Dale proceeded to explain the loss of fine structure in the following way: unperturbed benzene is planar in both the ground state and the excited state and the breathing mode is the main excited vibration. However, in distorted benzene the electronic distribution should vary in the two states and skeletal deformation vibrations perpendicular to the plane are allowed. The deformation vibrations overlap with the normal excited breathing vibrations causing a broad band. However, as Dale states, the ultraviolet and infrared spectra of 1,2,4-tri-t-butylbenzene are typically aromatic and distortion is small in these compounds.

The bathochromic shift in the ultraviolet spectrum for 1,2,4-tri-t-butylbenzene

is very small compared to the shift observed in ultraviolet spectra of highly strained systems such as 6,5,5,5-tetracyclic hydrocarbon (XV).



XV

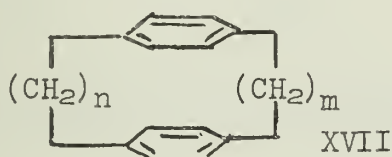


XVI

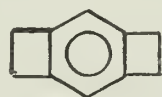
Rapoport and Smolinsky¹⁴ reported a bathochromic shift of 8 mμ with loss of fine structure for the 6,5,5,5-tetracyclic hydrocarbon compared with the 6,5,5-tricyclic hydrocarbon, (XVI). They attribute these differences in spectra to the additional strain associated with the fused cyclopentane ring system. If the ground state of the molecule is strained and raised in energy relative to the excited state, there should

be a lower transition energy and a bathochromic shift. Jaffe and Orchin¹⁵ suggested that the simplification of fine structure is due to the restriction of vibration introduced by the additional cyclopentane ring of XV.

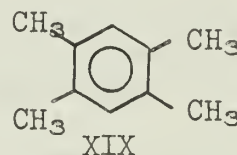
Similar ultraviolet spectra were noticed by Cram and coworkers¹⁶ in their spectral study of paracyclophanes. For compounds like XVII, as m and n decrease to two, the absorption band in the 240 to 280 mμ region tends to shift toward longer wavelength and lower intensity is observed. The fine structure also tends to be eliminated.



XVII



XVIII

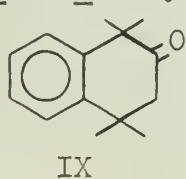


XIX

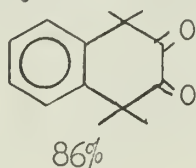
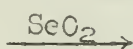
A striking exception to this behavior is seen in the ultraviolet spectrum of benzo[1,2:4,5]dicyclobutene (XVIII). Cava, Deana and Muth¹⁷ report that XVIII shows an appreciable bathochromic shift relative to durene (XIX) and ϵ_{\max} is ten times greater than that of XIX. In this case the vibrational fine structure is preserved.

Hübel and Hoogzand¹⁸ first prepared ortho-di-t-butylbenzene by heating the complex, $\text{Co}_2[(\text{CH}_3)_3\text{CC}\equiv\text{CC}(\text{CH}_3)_3]$ with acetylene. The n.m.r. spectrum showed two bands in the aromatic region and a single band at $\tau = 8.51$ ppm for the aliphatic hydrogens. Arnett and Strem¹⁹ also prepared ortho-di-t-butylbenzene in the same manner. The aromatic protons in their n.m.r. spectrum showed an A_2B_2 pattern in the region between 2.5 and 3.0 ppm. The aliphatic proton signal appeared at 8.67 ppm with an area 4.1 times that of the aromatic protons. (theory 4.5:1).

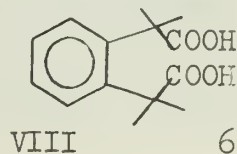
o-Di-t-butylbenzene has also been prepared using 1,1,4,4-tetramethyltetralone, as prepared by Bruson.⁶ Barclay, Hall and MacLean^{20,21} converted the tetralone to o-phenylene-di-isobutyric acid by permanganate oxidation and obtained a low yield of the acid with a melting point of 218-219°. Since Bruson reported a melting point of 181-183°, Barclay prepared the acid by an alternative route. Tetralone (IX) was oxidized with selenium dioxide to the diketone (86% yield) which was then oxidized by periodic acid to the acid (VIII, 64% yield). The acid synthesized in this manner had a melting point of 218-219°. The n.m.r. spectrum of the dimethylester of the acid showed a single band at 8.40 ppm for the C-methyl groups, a band at 6.39 ppm for the O-methyl groups and an A_2B_2 band pattern at 2.37 ppm for the four aromatic protons. The diester was subsequently reduced with LiAlH_4 to the diol. The diol was converted to the tosylate with p-toluenesulfonylchloride in pyridine and then reduced with LiAlH_4 . Vapor phase chromatography showed three major components, and was used to separate o-di-t-butylbenzene (XX) in 44% yield.



IX

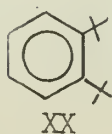


86%

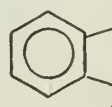
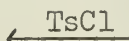
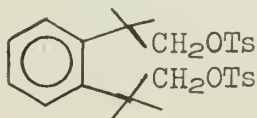


VIII

64%



XX

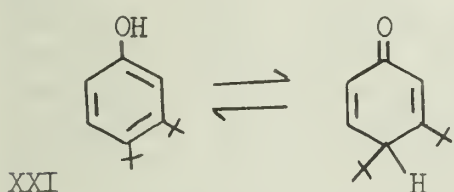


- (1) CH_2N_2
- (2) LiAlH_4

Burgstahler and Abdel-Rahmen²² have also prepared o-di-t-butylbenzene, using 1,1,4,4-tetramethyl-2-tetralone as the starting material. The same general synthetic procedure was employed. The ultraviolet spectrum for o-di-t-butylbenzene shows a loss of fine structure and a slight bathochromic shift relative to 1,1,4,4-tetramethyltetralin.²¹

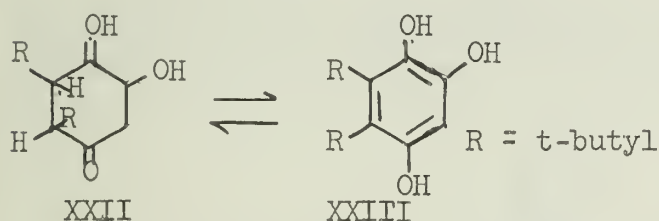
REACTIONS OF t-BUTYLBENZENES

Burgstahler and coworkers²³ prepared 3,4-di-t-butylphenol (XXI) from o-di-t-butylbenzene. Nitration of o-di-t-butylbenzene, followed by hydrogenation, yielded 3,4-di-t-butylaniline. The diazonium salt of the aniline was prepared and converted to the acetate upon slow solvolysis in acetic acid and acetic anhydride. Hydrolysis then gave the desired 3,4-di-t-butylphenol. The phenol did not react with 2,4-dinitrophenylhydrazine or semicarbazide hydrochloride to give a carbonyl derivative. The data suggested that the compound exists in the "enol" form, and that "the steric



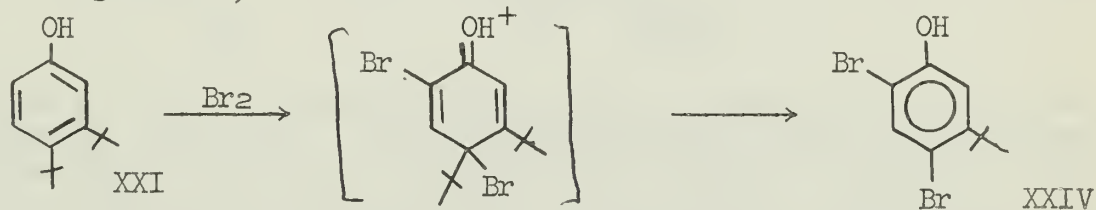
repulsion of the o-t-butyl groups in XXI is not sufficient to overcome the resonance stabilization of the benzenoid ring."

However, in 1959, Yohe²⁴ and coworkers reported that oxidation of 2,6-di-t-butyl-4-methylphenol gave optically active dl-trans-5,6-di-t-butyl-2-hydroxy-1,4-diketo-2-cyclohexene (XXII). The ease of racemization suggests that 5,6-di-t-butyl-1,2,4-trihydroxybenzene (XXIII) has a transient existence.



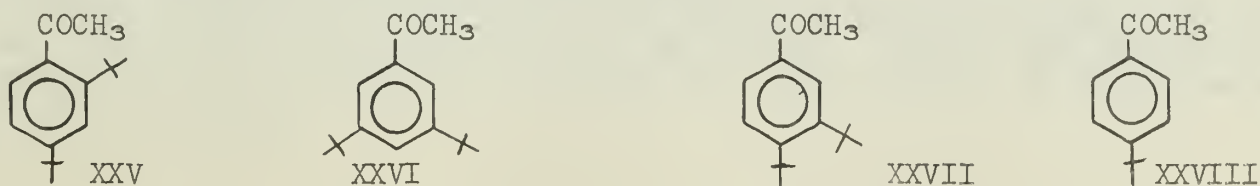
Burgstahler²⁵ more recently has reported that the reaction of bromine with 3,4-di-t-butylphenol (XXI) in CCl₄ or in acetic acid yields 2,4-dibromo-5-t-butylphenol (XXIV) rapidly. This suggests that a dienone intermediate is involved in the bromination.

In the same paper Burgstahler, Chien and Abdel-Rahman²⁵ described various chemi-



cal reactions of o-di-t-butylbenzene in more detail. Treatment of o-di-t-butylbenzene with concentrated nitric acid in acetic anhydride gave the mononitro product, 1,2-di-t-butyl-4-nitrobenzene, without rearrangement or loss of the t-butyl groups. When fuming nitric acid was used, the 4,5-dinitro derivative was formed. They found that o-di-t-butylbenzene nitrates 15% faster than t-butylbenzene. If the 4,5-dinitro derivative is heated under reflux with 30% potassium hydroxide solution for three days, no 2-nitro-4,5-di-t-butylphenol is obtained; however, o-dinitrobenzene yielded o-nitrophenol on refluxing for 3 hours in 5% potassium hydroxide solution. Burgstahler attributed this difference in reactivity to the retarding influence of the t-butyl groups.

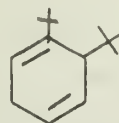
Acetylation of o-di-t-butylbenzene with acetyl chloride and aluminum chloride at 0° gave a mixture of four ketonic products plus some minor hydrocarbons. The hydrocarbons were shown to be m- and p-di-t-butylbenzene and 1,3,5-tri-t-butylbenzene, with the aid of n.m.r. and infrared spectra. The ketonic products were separated by chromatography on silica gel. The acetophenones, XXV, XXVI, XXVII, XXVIII, were present in approximately 2:1:3:2 ratio, respectively.



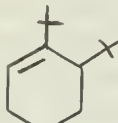
Alkylation with t-butylchloride in aluminum chloride led to extensive isomerization of o-di-t-butylbenzene. Products found were 1,3,5-tri-t-butylbenzene and p-di-t-butylbenzene.

In the presence of aluminum chloride in carbon disulfide at 0°, o-di-t-butylbenzene isomerizes to give p- and m-di-t-butylbenzene in a ratio of 3:1 in only three minutes.

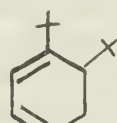
Reduction of o-di-t-butylbenzene in the presence of a suitable proton source with lithium in liquid ammonia yielded 2,3-di-t-butyl-1,4-cyclohexadiene (XXIX) and 2,3-di-t-butylcyclohexene (XXX). With isopropyl alcohol as the proton source, the



XXIX



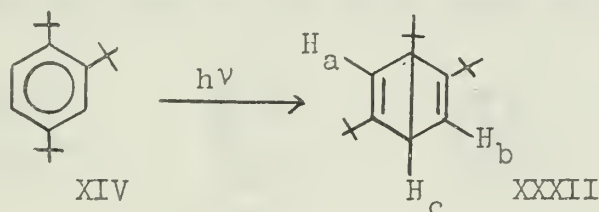
XXX



XXXI

ratio of XXIX to XXX was approximately 9 to 2; while with t-butyl alcohol, the predominate product was in general XXX. With lithium ethylamide in ethylamine XXIX can be further isomerized to 1,6-di-t-butyl-1,3-cyclohexadiene (XXXI). Since XXIX can be isomerized easily into XXXI, Burgstahler suggests that the predominate formation of XXX, when t-butyl alcohol is the proton source, may reflect the greater base strength of the t-butoxide ion. The t-butoxide ion should be able to isomerize the double bonds of XXIX into conjugation. Further attack by lithium would then lead to XXX.

Recently papers have appeared on the photochemical reactions of t-butyl benzenes. In a communication, Van Tamelin and Pappas²⁶ reported that the irradiation of ether solutions of 1,2,4-tri-t-butylbenzene (XIV) gives what they believe to be 1,2,5-tri-t-butylbicyclo[2.2.0]hexa-2,5-diene (XXXII).



The hydrocarbon obtained from the irradiation using a Vycor filter had a parent peak of 246 in the mass spectrum. The n.m.r. spectrum showed three peaks of equal intensity: a singlet peak with minor shoulders at 3.87, a doublet at 3.95 and a doublet at 6.80. These peaks were assigned to H_a, H_b, and H_c protons, respectively. A singlet at 8.94 with a relative intensity of 9 was attributed to one t-butyl group while another singlet at 9.02 with an area of 18 was assigned to two t-butyl groups.

Burgstahler and coworkers²⁷ irradiated dilute ether solutions of o-di-t-butylbenzene using an all quartz mercury light source. In a typical run, they reported complete isomerization of o-di-t-butylbenzene in approximately 70 hours to 50% meta and 50% para isomers. After 140 hours, the product distribution was 80% para and 20% meta. However, the yield of para and meta isomers constituted only 20% of the original starting material. Isomer ratios were determined from characteristic absorption peaks in the n.m.r. and/or infrared spectra.

Irradiation of a mixture of t-butylbenzene and 1,3,5-tri-t-butylbenzene produced no detectable amount of the di-t-butyl isomer. This suggests that the photochemical isomerization is intramolecular. Furthermore the photochemical reaction did not seem to be affected by photosensitizers. Burgstahler suggests that "these isomerizations can be accounted for either by photoinitiated 1,2 migration of a t-butyl group or by excitation of the benzene ring to a Ladenburg-type structure with subsequent rearomatization to form meta and thence the para isomer".

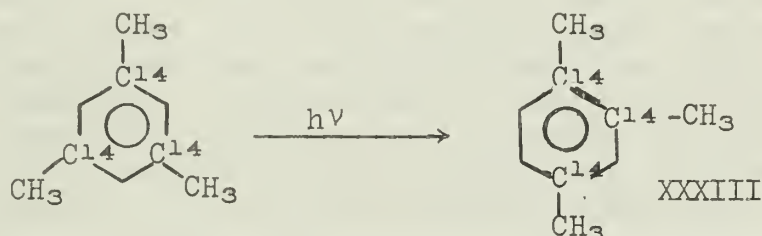
In the photochemical irradiation of the vapors of xylenes, Wilzbach and Kaplan²⁸ observed isomerization and polymerization taking place. With a high pressure mercury lamp (Hanovia 673-A) at pressures of 5-7 mm. in a Vycor vessel, the following major products were observed.

Reactants

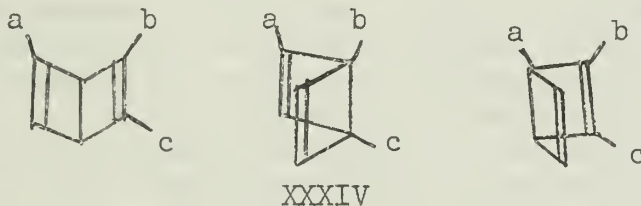
<u>Products</u>	<u>o-xylene</u>	<u>m-xylene</u>	<u>m-xylene</u> (in presence of N ₂)
<u>o</u> -xylene	81.3%	1.09%	0.81%
<u>m</u> -xylene	3.66	85.5	91.6
<u>p</u> -xylene	0.20	4.1	2.81
polymer	13.1	8.8	
time (min)	60	30	30

The remainder of the products consisted of hydrogen, methane and molecules made by methyl or hydrogen migration. In the presence of foreign gases the ratio of o-to p-xylene is relatively constant for the photoisomerization of m-xylene.

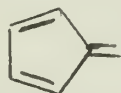
In a recent communication Kaplan and coworkers²⁹ described the photochemical rearrangement of an isotopically labelled aromatic system. They found that mesitylene-1,3,5-C¹⁴ (from acetone -2-C¹⁴) yielded 1,2,4-trimethylbenzene labelled exclusively in the 1, 2, and 4 positions, XXXIII.



They proposed three possible mechanistic interpretations for this observation. In one alternative, conversion to three bent Dewar structures (XXXIV) with different bonding was suggested. Interconversion of the three forms under the prevailing excitation is required.



A second possibility is conversion of the excited aromatic molecule to a fulvene (XXXV) followed by a re-aromatization. However, fulvene has been reported not to revert to benzene.³⁰ Finally, twisting of a pair of ring carbons out of plane through 180° would give an intermediate like XXXVI. The authors point out, however, that no single mechanism seems to explain why only 1,2 shifts of dimethylbenzenes are observed in the vapor phase photolysis while 1,3 and 1,2 shifts are observed in the photolysis of solutions.

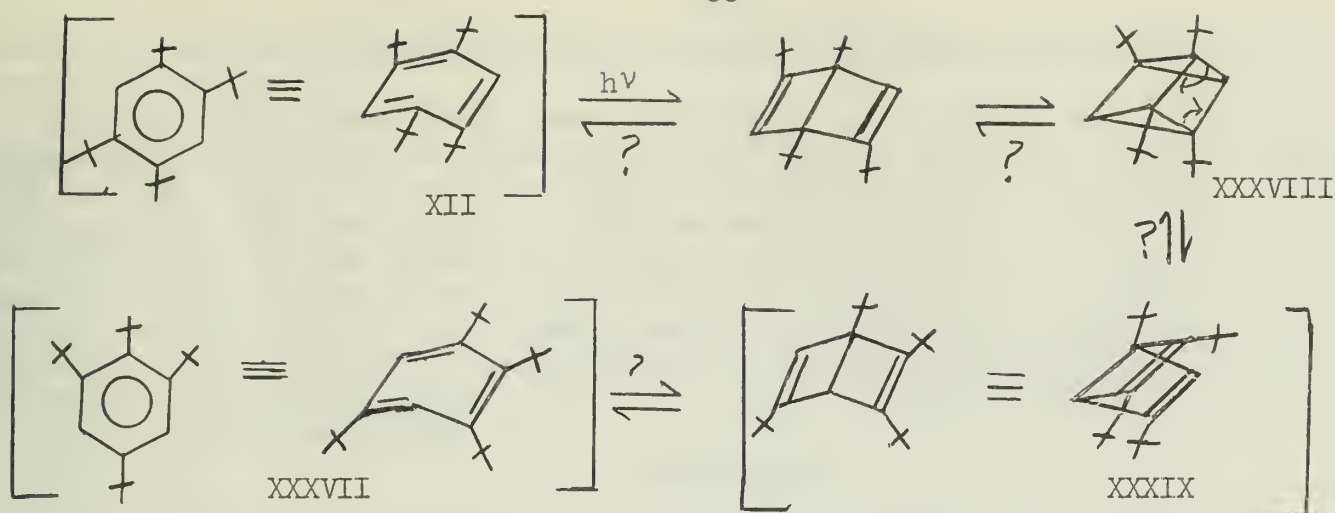


XXXV



XXXVI

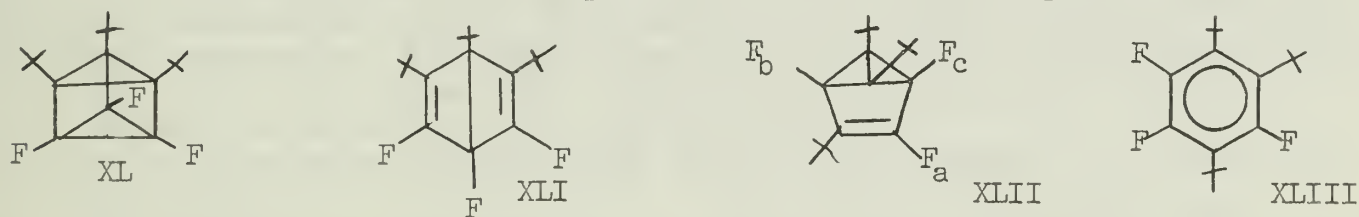
Arnett and Bollinger³¹ have reported that the photoisomerization of 1,2,4,5-tetra-t-butylbenzene (XII) produces 1,2,3,5-tetra-t-butylbenzene (XXXVII) in 11% yield. Migration of a t-butyl group to a more crowded position seemed unlikely, so the following rearrangement through the Ladenburg benzene structure (XXXVIII) was proposed.



The n.m.r. spectrum of XXXVII in carbon tetrachloride showed an aromatic singlet at $\tau = 3.07$ ppm and three peaks at $\tau = 8.72$, 8.61 and 8.59 ppm in the methyl region. The methyl peaks had an area 18 times that of the aromatic peak. Compound XXXVII was converted to 1,3,5-tri-*t*-butylbenzene upon heating 30 minutes at $300 \pm 10^\circ$ while XII was stable under the same conditions. Compound XXXVII formed white crystals in an oil and the oil remaining showed n.m.r. and spectral properties of XXXIX. The n.m.r. spectrum has four peaks in the methyl region at $\tau = 8.83$, 8.85 , 8.97 and 9.08 . A vinyl doublet at $\tau = 4.06$ ppm had $J = 1.2$ cps and methine doublet at $\tau = 6.92$ ppm had $J = 1.2$ cps.

Viehe, Oth, and Valange³² reported the formation of 1,2,3-tri-*t*-butyltrifluorobenzene by the spontaneous trimerization of *t*-butylfluoroacetylene. They found *t*-butylfluoroacetylene, made from dehydrohalogenation of fluorohalogenoethylenes, could be kept only at low temperatures. At 0° , the liquid acetylene spontaneously and exothermically forms oligomers which are mainly trimers. The major crystalline portion of the oligomers appears to be 1,2,3-tri-*t*-butyltrifluorobenzene, on the basis of n.m.r. The fluorine n.m.r. spectrum (int. std. trichlorofluoromethane) showed a doublet at $+127.7$ ppm with relative intensity of two and a triplet at 154.8 ppm with relative intensity of one. The proton n.m.r. spectrum (int. std. TMS) showed a multiplet at $\tau=8.55$ ppm with relative intensity of two and a singlet at $\tau=8.61$ ppm with relative intensity of one.

In a later communication Viehe and coworkers³³ claimed to have isolated and identified the following isomeric products from the same oligomeric mixture.



The identification is based on the following experimental data. The proton n.m.r. spectra are based on TMS internal standard and the fluorine n.m.r. spectra are based on trichlorofluoromethane.

The Ladenburg benzene derivative (XL) was isolated by gas chromatography and was stable up to 250° with a melting point of 187° . The infrared spectrum shows no C=C absorption and the ultraviolet spectrum down to 200 m μ shows only end absorption. The proton n.m.r. spectrum has a singlet at $\tau=8.32$ ppm and the fluorine n.m.r. spectrum has a singlet at $+176$ ppm. No reaction is observed with bromine in CCl_4 or with ozone in petroleum ether at room temperature. An X-ray analysis is reportedly being done.

Compound XLI, 1,2,6-tri-*t*-butyltrifluorobicyclo[2.2.0]hexa-2,5-diene, was separated from XL only partially by careful crystallization. On brief heating at 100° , XLI can be converted to 1,2,3-tri-*t*-butyltrifluorobenzene. With approximately 30% XL present, the proton n.m.r. spectrum contains 2 peaks at $\tau=8.8$ and 8.88 ppm with a relative intensity of 2 to 1 and the fluorine n.m.r. spectrum contains 2 peaks at $+103$ and $+181$ ppm with a relative intensity of 2 to 1. The ultraviolet

shows only end absorption down to 200 mμ and the infrared spectrum shows C=C absorption at 5.96 μ.

Compound XLII, which they named benzvalene, is a liquid separated by column chromatography. Benzvalene shows strong C=C absorption in the infrared spectrum at 5.98 μ. The ultraviolet spectrum shows two maxima at 232 mμ ($\epsilon_{\text{max}}=2500$) and at 300 mμ ($\epsilon_{\text{max}}=300$). The proton n.m.r. spectrum has two signals: a doublet at $\tau=8.78$ ppm and a multiplet at $\tau=8.84$ ppm with relative intensity of 1 to 2. The fluorine n.m.r. spectrum has three signals of equal intensity: a broad band at +102 ppm (F_A), a doublet at +182 ppm (F_B) and a quadruplet at +184 ppm (F_C). Benzvalene forms a dibromide with no peaks in ultraviolet and no C=C peak in the infrared spectrum. De-bromination yields benzvalene again. On heating benzuvalene forms 1,2,4-tri-t-butyltrifluorobenzene (XLIII).

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ELECTROLYTIC HYDRODIMERIZATION

Reported by Donald S. Hetzel

July 23, 1965

INTRODUCTION

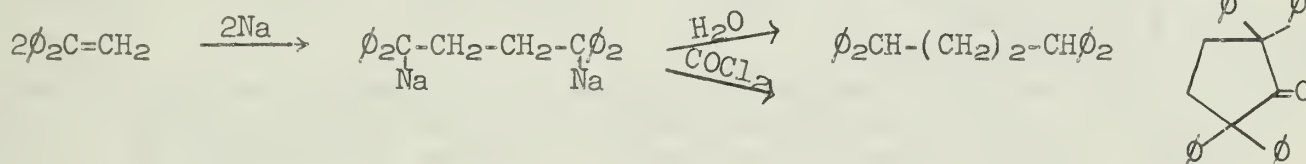
The electrochemistry of organic compounds has been studied for more than a century and many unique transformations have been observed.¹ Aside from the Kolbe reaction, though, few electrochemical techniques have found wide synthetic application. Recently, however, considerable attention has been devoted to the electrolytic hydrodimerization reaction probably because of the very attractive commercial possibilities.

Knunyan² coined the term hydrodimerization to describe the following transformation where X is an activating group such as -CN, -CO₂R or -COR. Either alkali metals or an electric current may supply the needed electrons while the requisite protonation can occur under the reaction conditions or during aqueous workup.

Commercial interest in this process is readily apparent since acrylonitrile (X = CN) may be converted to adiponitrile, a key Nylon intermediate.

DISCUSSION

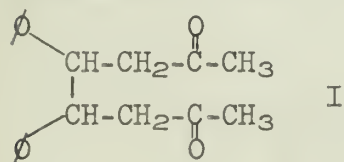
Hydrodimerization was observed by several early workers investigating organometallics. Sodium metal adds to some olefins to give disodio derivatives which form bimolecular reduction products upon hydrolysis.³ Schlenk and Bergmann,⁴ for example, recognized that 1,1-diphenyl ethylene reacted with sodium to give a bimolecular product. Similarly, 9-benzal fluorene gives a hydrodimer upon treatment



with sodium. Unfortunately, no yields are reported for these reactions so a judgment of reaction efficiency can not be made. A very unusual reductive dimerization has been reported by Kohler and Drake⁵ who found that attempted hydrogenation of β -nitrostyrene over platinum led mainly to diphenyl dinitro butane. This appears to be an isolated example, however, for all attempts to extend the reaction to similar nitro compounds failed.

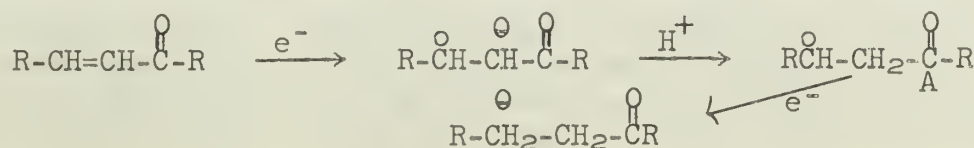
HYDRODIMERIZATION OF α,β -UNSATURATED KETONES

The electrochemistry of unsaturated ketones has not been studied extensively. An early report by Law⁶ suggests that mesityl oxide electrolyzed in acidic ethanol gave a poorly characterized mixture of higher molecular weight products and relatively little reduced monomer, i.e., methyl isobutyl ketone. More recently, Pasternak⁷ has examined the electrochemistry of some aryl and alkyl substituted unsaturated ketones. He found that electrolysis of benzalacetone, for example, at low pH(1.3) gave a hydrodimer (I) in high yield. At higher pH only monomeric



reduction product, benzylacetone, was formed. Benzalacetophenone, dibenzalacetone and mesityl oxide gave similar hydrodimers. From polarographic studies he concluded that reduction occurred via two single electron transfers. This observation suggests some possible reaction pathways. The radical A could desorb from the cathode and unite with a

second identical radical species or it could pick up a second electron to form a

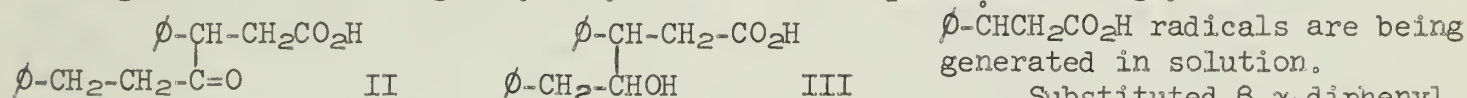


β -carbanion which then attacks a second ketone molecule in a Michael-type addition. Insufficient data are available here for a choice between these two possibilities, but both have been observed in other systems.

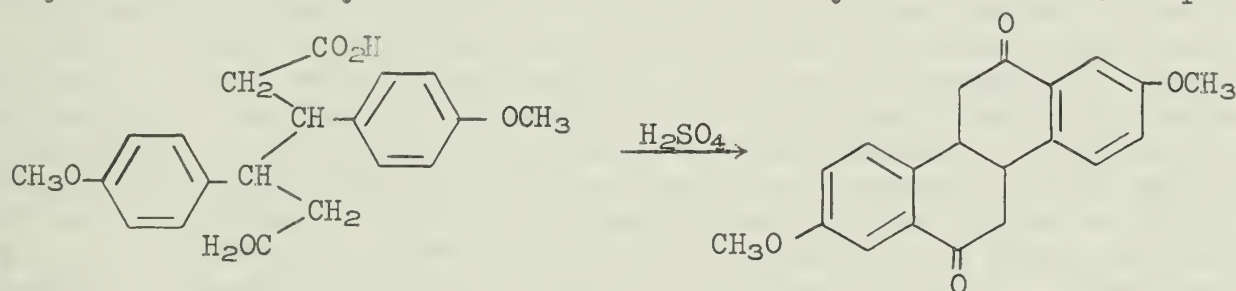
HYDRODIMERIZATION OF α,β -UNSATURATED ACIDS

Wilson has extensively studied the electrochemistry of unsaturated acids. Sorbic acid was found to form a mixture of unsaturated bimolecular products almost quantitatively upon electrolysis in acid solution.⁸ Cathodes of high overvoltage favored hydrodimerization, an observation that led Wilson to conclude that adsorbed

$\text{CH}_3\text{-CH=CH-CH=CH-CO}_2\text{H} \xrightarrow[2\text{H}^+]{2\text{e}^-}$ $\begin{array}{c} \text{CH}_3\text{-CH=CH-CH-CH}_2\text{-CO}_2\text{H} \\ | \\ \text{CH}_3\text{-CH=CH-CH-CH}_2\text{-CO}_2\text{H} \end{array}$ sorbic acid molecules picked up a single electron and proton to give an intermediate radical which then desorbed and reacted with a second radical species. Further studies with cinnamic acid supported this hypothesis.⁹ The expected hydrodimer of cinnamic acid, β,γ -diphenyl adipic acid, was formed in moderate yield (55%) when the electrolysis was performed in acidic solution using a mercury cathode. Meso and dl acids were found in approximately equal amounts. An examination of substituent effects suggested that substitution affected the process of adsorption on the cathode, but apparently had little effect on stability of the intermediate radical.¹⁰ Adipic acid formation was always complicated by production of a complex mixture of partially polymerized materials easily separated from the adipic acids by benzene extraction. Subsequent investigation¹¹ showed that the mixture contained II, III and higher molecular weight hydroxy acids. These products strongly indicate that

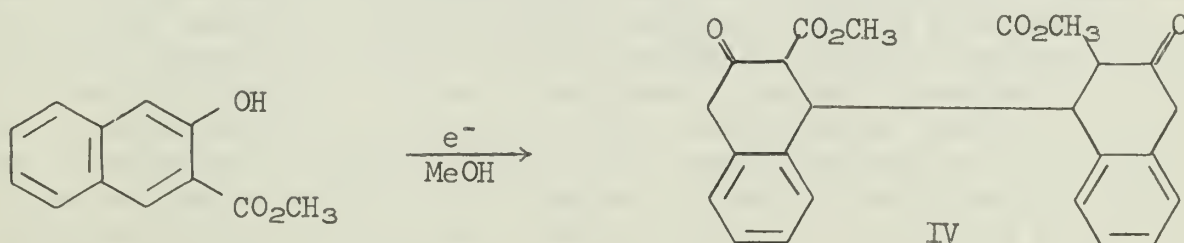


Substituted β,γ -diphenyl adipic acids have been sought by other workers as intermediates in hormone syntheses since they can be readily cyclized to chrysenes which are known to have estrogenic activity. The synthetic utility of the electrolytic method is illustrated by these studies. Diphenyl



adipic acids generally have been prepared by a double Reformatsky reaction (overall yield less than 10%) or by a bimolecular reduction of cinnamic esters with aluminum amalgam (highest yield 24%).¹² The electrolytic method, in comparison, gives a 55% yield of pure material.

Belov, et al.¹³ report the reductive dimerization of naphthol carboxylic acids to give ketodiester of type IV. Yields are low (24%) and several unidentified byproducts are formed. Tomilov¹⁴ has examined the cathodic hydrodimerization of



acrylate and maleate esters. Methyl acrylate electrolyzed in alkaline solution at a graphite cathode gave about 14% of the hydrodimer, dimethyl adipate. Dimethyl maleate formed its hydrodimer, 1,2,3,4-tetracarboxymethoxybutane, in only 4.7% yield. Somewhat surprisingly, methyl esters gave higher yields than ethyl esters. No explanation for this observation was advanced.

Much of the current interest in electrolytic hydrodimerization stems from Knunyants' studies with electrically generated amalgams in which he showed that α,β -unsaturated acids and their derivatives could be effectively hydrodimerized.^{15,16} The most striking result was the conversion of acrylonitrile to adiponitrile in 62% yield without attendant polymerization. Previous attempts to effect this conversion with sodium in water¹⁷ or magnesium in methanol¹⁸ had been only marginally successful. Knunyants' procedure consisted of electrolyzing alkali hydroxides at a mercury cathode. The reducible substance was suspended or dissolved in mineral acid solution above the cathode thereby permitting contact with the amalgam generated. Table I summarizes results obtained with various substrate-amalgam combinations.¹⁶

Table I		Hydrodimer Yield, %
Substrate	Amalgam	
$\text{CH}_2=\text{CHCO}_2\text{Et}$	K/Hg	52
$(\text{CH}_3)_2\text{C}=\text{CHCO}_2\text{Et}$	"	0
$\text{CH}_2=\text{C}(\text{CH}_3)\text{CO}_2\text{Et}$	"	23
$\text{CH}_3\text{CH}=\text{CH}-\text{CN}$	K/Hg or Na/Hg	0
"	Li/Hg	37
$\text{EtO}_2\text{C}-\text{CH}=\text{CH}-\text{CO}_2\text{Et}$ (cis)	K/Hg	7.3
" (trans)	"	28.6
$\phi-\text{CH}=\text{CH}-\text{CONEt}_2$	"	22.7

Knunyants concluded that hydrodimer yields increased with increasing potential of the amalgam ($\text{Li/Hg} > \text{K/Hg} > \text{Na/Hg}$) and were decreased by interrupted conjugation between activating groups and ethylenic units. Thus maleate formed less hydrodimer than the more highly conjugated fumarate. Steric crowding at the β -position also drastically lowered yields. Knunyants interpreted his findings in terms of a free radical intermediate which dimerized to the observed products, a scheme identical to that suggested by Wilson in the cinnamic acid study. The validity of this proposal may be questioned, however, in view of the absence of polymer formation. Also when $\text{C}_2\text{D}_5\text{OH}$ was used as the solvent for the hydrodimerization of ethyl acrylate, no deuterated ethyl propionate could be detected. These inconsistencies were rationalized by suggesting that radicals at a cathode differ from radicals in solution.

Certain drawbacks are inherent in this amalgam procedure. Functional groups sensitive to alkali metal attack such as $-\text{CONH}_2$ are not compatible. Addition of alkali metal to the olefin is a distinct possibility and should this compete favorably with coupling, dihydro product would predominate. Solubility in the aqueous mineral acid solution could be a problem. Compounds of low solubility would not be expected to react appreciably. One is also limited in this procedure by the cathode potential which can be obtained since alkali metal cations begin to discharge to a mercury cathode at about -1.9 v. (vs. S.C.E.).¹⁹ Compounds with reduction potentials more negative than -1.9 v. could not then be reduced.

Realizing the disadvantages and unfavorable economics of the Knunyants procedure, Baizer and his group²⁰ set out to develop an economically feasible process for hydrodimerizing acrylonitrile (AN) to adiponitrile (ADN). Several difficulties were anticipated. Cathodic polymerization of AN in acidic solution was known.²¹ An aqueous system was desired and AN is not water soluble. Furthermore, if hydrodimerization were to occur, AN concentration must be high in order to compete effectively for the carbanions formed at the cathode. Initial experiments with aqueous alcoholic potassium acetate and with phosphate buffer solutions were unsuccessful. The "hydrotropic" solvents developed by McKee²² provided an initial answer. These solvents are concentrated aqueous solutions of alkali aryl sulfonates and possess an astonishing ability to "salt in" organic materials of low solubility. Table II presents some solubility data compiled by Booth²³ to illustrate this point.

By using a saturated solution of equimolar quantities of sodium and potassium *p*-toluenesulfonates, AN concentrations up to 21% could be realized.²⁴ When these solutions were electrolyzed at a mercury cathode, ADN was indeed formed without polymerization. Propionitrile (PN), however, was the main product and, if the pH was not kept low, significant amounts of bis-2-cyanoethyl ether were found. Although increasing AN concentration to saturation (21%), increasing the current

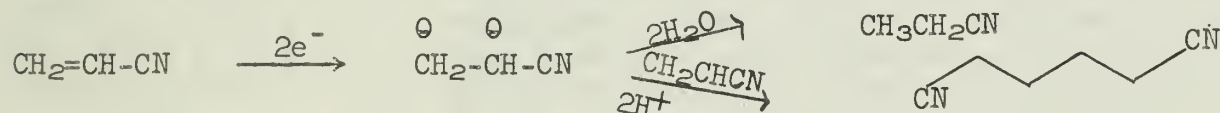
Table II

Compound	ml. dissolved in 100 ml. distilled H ₂ O	ml. dissolved in 100 ml. 40% xylene sulfonate soln.
Acetophenone	0.54	29.6
Aniline	3.8	>400
Chlorobenzene	<.02	1.6
Diethyl ether	8.0	15.8
Nitrobenzene	0.10	5.6
Mesitylene	<.02	0.50

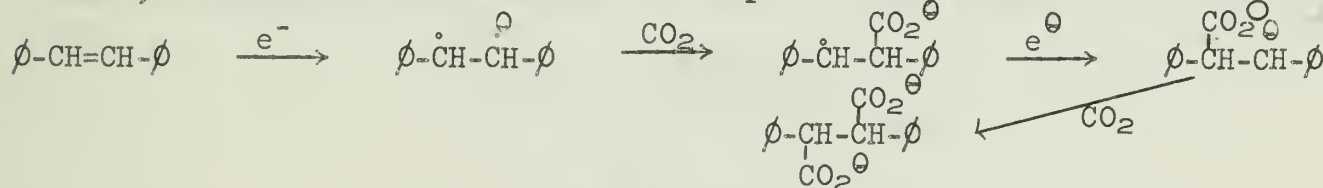
density and maintaining pH control by continuous acetic acid addition raised ADN yields relative to PN, considerable PN was still formed and ADN yields could not be raised above 63%.

The similarity of this figure to the yield reported by Knunyants (62%) and the observation that ADN/PN ratios were strongly dependent on the alkali metal cation present suggested an explanation for the persistent PN formation. Platanova reports²⁵ that the polarographic wave for AN has $E^1/2 = -2.05$ v.(vs. S.C.E.). As mentioned previously, the alkali metal ions will discharge at this voltage. Two competing processes could then be operative; direct electrochemical reduction leading to ADN and alkali metal addition to AN giving an organometallic which is readily hydrolyzed to PN. Substitution of quaternary ammonium ions (Et_4N^+ , $E^1/2 = -2.4$ v.²⁶) for the alkali cations removed this last stumbling block. Using a 40% AN solution in 56% aqueous tetraethylammonium *p*-toluenesulfonate and a mercury cathode, quantitative conversion of AN to ADN was achieved with 100% current efficiency. The process could be made continuous by using a Soxhlet extraction type procedure in which excess AN was refluxed into the reaction vessel to dissolve the ADN and remove it as formed. With engineering refinements,²⁷ this process is currently being commercialized for economical ADN production.²⁸

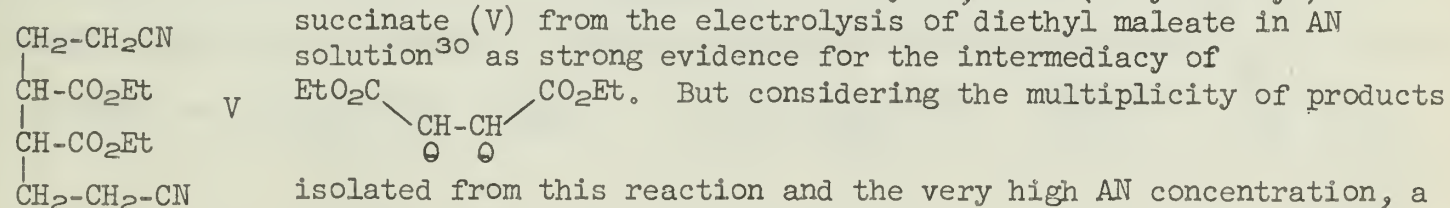
Baizer suggested that the reaction was best explained by the following mechanism involving a dicarbanion intermediate. The results could also be accommodated by a



stepwise mechanism similar to that proposed by Wawzonek²⁹ for the electrolysis of stilbene in the presence of CO₂. The product isolated was diphenyl succinic acid. With AN, the anion radical would be first protonated, then absorb a second electron



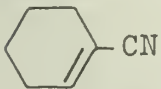
to form a β -carbanion which attacks a second AN molecule as in a typical Michael reaction. Baizer considers the isolation of diethyl α,α' -bis(2-cyanoethyl)

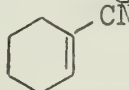


isolated from this reaction and the very high AN concentration, a sequential reaction still seems possible. It would seem difficult to chemically distinguish these two pathways, but one is intuitively prejudiced against the dicarbanion scheme. Apparent simultaneous adsorption of two electrons has been observed with azobenzene.³¹ The presence of "free" radicals is not indicated since polymerization is not observed even with compounds like 2-phenyl butadiene³² known to be very susceptible to radical attack.

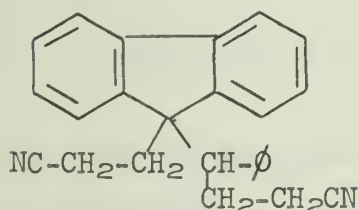
Baizer has explored the broader synthetic utility of electrolytic hydro-dimerization. Using unsaturated acids and their derivatives as substrates, he

obtained considerably higher yields³³ than Knunyants reported using his amalgam procedure. Some representative results are summarized in Table III.

Compound	Table III	
	% Hydrodimer by Amalgam Process	% Hydrodimer by Electrolytic Process
CH ₂ =CHCO ₂ Et	52	74-87
(CH ₃) ₂ C=CHCO ₂ Et	0	66
EtO ₂ C-CH=CHCO ₂ Et (cis)	7.3	61.5
CH ₂ =CH-CONH ₂	0	39.6
	-	66.4
(CH ₃) ₂ C=C(CH ₃)CN	-	0
CH ₃ -CH=CH-CO ₂ Et	-	90

Many of the amalgam drawbacks have been surmounted. Successful reaction of unprotected amides is possible. Shielding of the β-position is no longer deleterious, although α-substitution hinders the reaction. Solubility is no longer a problem and compounds with quite negative reduction potentials ($E^1/2$ for  = -2.2 v.) are successfully dimerized.

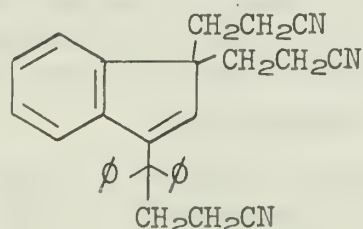
The possibility of utilizing this reaction to prepare unsymmetrical hydrodimers, such as cyanoesters or esteramides, by the mixed coupling of two substrates is most attractive. Successful mixed electrolytic couplings are rather rare. Allen³⁴ has reported a mixed pinacol reduction of p-methoxy- and p-dimethylamino acetophenones in which unsymmetrical product was isolated in 38% yield. Crossed Kolbe reactions have also been exploited successfully.³⁵ Electrolysis of 9-benzalfluorene alone led to the known hydrodimer in 66% yield.³² When a benzalfluorene - AN mixture (1:10) was electrolyzed, a dicyanoethylated product identified as VI was obtained 76% yield.



VI

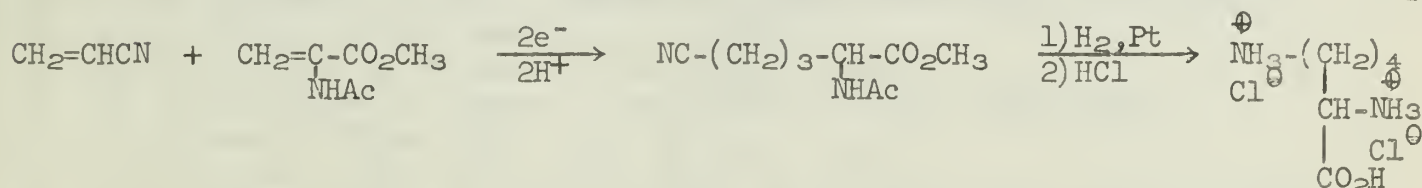
It is significant to note that under the usual Michael conditions, 9-benzylfluorene could not be cyanoethylated.³⁶ Here then is a way of generating carbanions not obtainable by proton abstraction from the corresponding hydrocarbon. Attempted hydrodimerization of 8,8-diphenyl benzofulvene was unsuccessful, probably because of steric crowding in the intermolecular addition step; but in the mixed

coupling with AN, a tricyanoethylated product VII was formed. An interesting

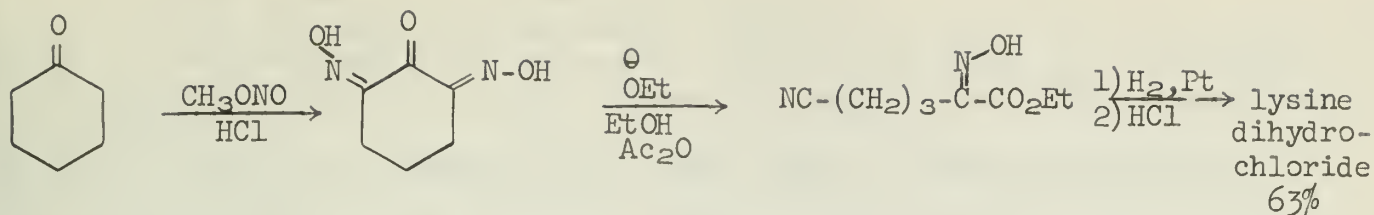


VII

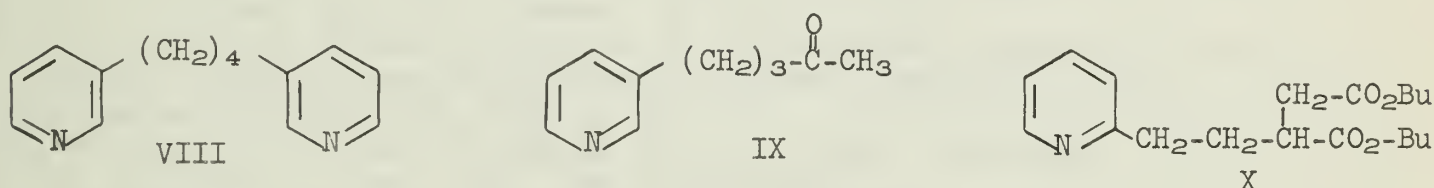
lysine synthesis was developed based on the mixed hydrodimerization.³² No attempt



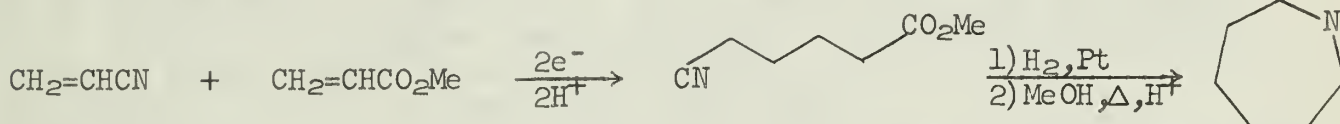
to optimize yields was made and undoubtedly use of an α-aminoacrylate moiety having a more positive reduction potential ($E^1/2$ = -1.75 v. for compound used) would raise the cyanoamino valerate yield since some ADN was formed from AN reduction. The simplicity inherent here can be realized by considering another lysine synthesis beginning with cyclohexanone.³⁷



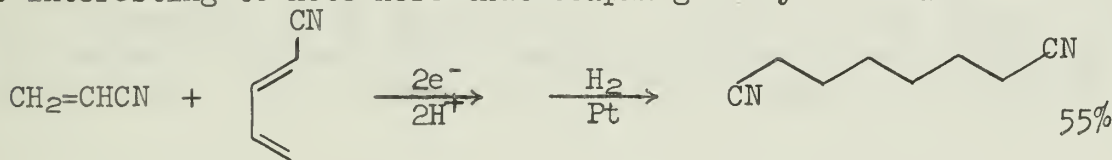
Both 2- and 4-vinylpyridine were found to be good substrates for hydrodimerization since the vinyl group was reduced before the ring.³⁸ Thus the hydrodimer of 4-vinylpyridine (VIII) could be obtained in 82% yield. Mixed couplings between 4-vinylpyridine and methyl vinyl ketone to give IX and between 2-vinylpyridine and dibutyl maleate to give X were quite successful. The latter compound could be converted to ketoquinolizidine by reduction and ring closure.



Commercially valuable E-caprolactam³⁹ and sebaconitrile³² are also available by the hydrodimerization route.



It is interesting to note here that coupling to cyanobutadiene occurred by attack



at the δ -position as was noted when cyanobutadiene itself was hydrodimerized.⁴⁰

CONCLUSIONS

The commercial importance of electrolytic hydrodimerization has been demonstrated. Its value to the synthetic chemist lies in the crossed coupling modification by which unsymmetrical dimers can be readily obtained. Further extension of reaction scope and efficiency should be possible.

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BICYCLOBUTANES

Reported by Manley R. Johnston

July 28, 1965

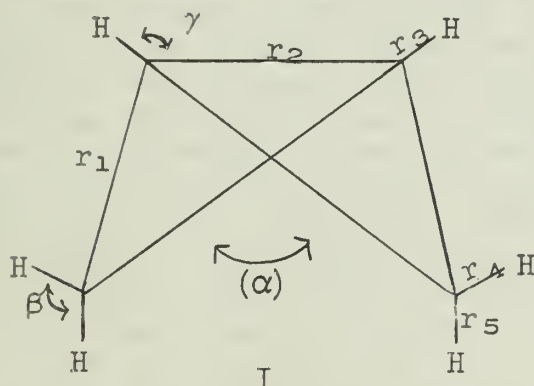
A report of a bicyclo[1.1.0]butane* synthesis was made as early as 1910, when Guthzeit and Hartman claimed the successful preparation of ethyl-2,2,4,4-tetra-carboxybicyclobutane-1,3-dimalonate.¹ Beesly and Thorpe subsequently reported 1-methyl-2,3,4-tricarboxybicyclobutane,² however, later workers found this work irreproducible.³ No further references to the synthesis of these compounds were made until 1959, when Wiberg and coworkers described the synthesis of ethyl-bicyclobutane-1-carboxylate,⁴ the first authentic bicyclobutane. Since that time these compounds have commanded considerable attention in the chemical literature.

The study of this molecular skeleton has proven important in ascertaining the role of strain in determining the chemical and physical properties of cyclic compounds. This seminar will deal with the structure, strain determinations, thermal isomerizations, chemical reactions and acidity of the bridgehead hydrogens of this highly strained molecule.

The synthesis of these compounds has been recently reviewed.^{5,6} Carbenoid addition to the appropriate olefin or paraffin⁷⁻¹⁸ is the method most generally used, although dehalogenation,¹⁹ dehydrohalogenation^{4,20,21} and electrolysis of cyclobutanes,²² as well as photolysis of 1,3-butadienes all lead directly to bicyclobutanes.^{23,24}

The vibrational spectrum of bicyclobutane has been studied by Haller and Srinivasan.²⁵ The coincidence of some of the Raman and infrared frequencies has been used to exclude a planar carbon skeleton, and in its place these workers propose a molecule possessing C_{2v} symmetry, which allows absorption both in the Raman and infrared.

From the rotational fine structure, some of the geometrical parameters were evaluated by invoking certain assumptions a priori. They assumed that the cyclopropane rings in bicyclobutane resembled those in the isolated cyclopropane molecule and that the molecular dimensions in the bicyclic compound were identical to those in cyclopropane. It was assumed further that each H-C-H angle (β) was bisected by the plane of the ring to which it was attached, and finally that the C-C-H angle (γ) is linearly related to the angle between the cyclopropane rings between the linear limit of 180° and the tetrahedral limit of 144.4° . By varying the angle and r_2 between limits of $88-180^\circ$ and $1.50-1.56 \text{ \AA}$, respectively, these workers computed approximate synthetic vibration-rotation spectra and compared them to the observed fine structure. They then evaluated the remaining molecular constants from the synthetic spectrum which most closely coincided with the observed spectra. The structure they propose from this study is diagrammed below.



Assumed parameters

$$\begin{aligned} r_1 &= 1.53 \text{ \AA} \\ r_3 &= r_4 = r_5 = 1.08 \text{ \AA} \\ \beta &= 118^\circ \end{aligned}$$

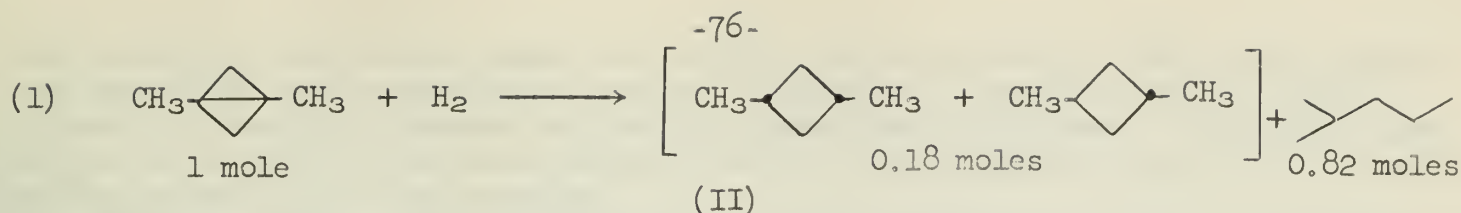
Calculated

$$\begin{aligned} r_2 &= 1.54 \pm 0.02 \text{ \AA} \\ \alpha &= 126 \pm 3^\circ \\ \gamma &= 163 \pm 3^\circ \end{aligned}$$

Many of the unusual properties of this molecule can be attributed to the reactivity of the 1,3-bond, made accessible by a lowering of the transition state energy by release of strain. The strain inherent in the bicyclobutyl systems is, therefore, one of

the molecule's⁷ most interesting properties. Doering²⁶ and co-workers have estimated the total strain of 1,3-dimethylbicyclobutane (II) from the heat of hydrogenation. Using the heat of formation of 1,3-dimethylcyclobutane and 2-methylpentane, they calculate the heat of formation of 1,3-dimethylbicyclobutane as 38.5 kcal/mole. Using Franklin's group equivalent values,²⁷ they estimate a heat of formation of -28.5 kcal/mole for a similarly substituted unstrained analog. The total strain

*Throughout the rest of the discussion, bicyclo[1.1.0]butane will be designated as bicyclobutane.

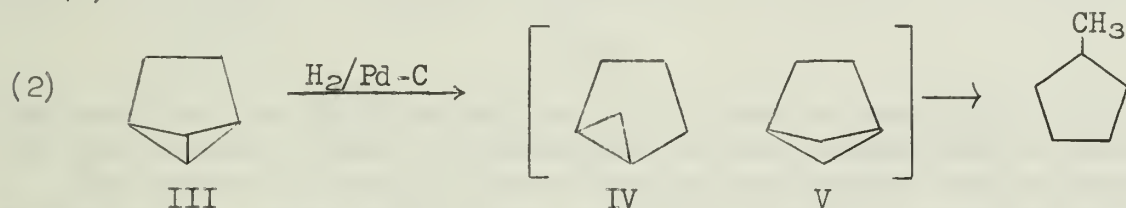


in the molecule, equated to the difference between the hypothetical "strain-free" molecule and that actually found is 67.0 kcal/mole. The strain energy of 16.7 kcal/mole/carbon atom is the highest found thus far.

Doering and co-workers also estimate the strain relieved on hydrogenation of the C₁-C₃ bonds and the C₁-C₂ bonds by calculating the heats of formation of 1,3-dimethylcyclobutane and 1,1,2-trimethylcyclopropane, the products which would arise from hydrogenation of the 1,3 and 1,2-bonds, respectively. From this they estimate a heat of hydrogenation for each molecule. Comparing heats of hydrogenation of similarly substituted strain free carbon-carbon bonds, they propose the strain relieved by hydrogenation of the 1,3 and 1,2-bond to be 41.3 and 39.9 kcal/mole, respectively.

Hydrogenation of bicyclobutanes has been used as evidence of their existence. These compounds readily undergo hydrogenation, absorbing two moles of hydrogen to give the corresponding monocyclic and acyclic compounds.

Lemal and Shim¹⁷ have shown that the two bonds in tricyclo[2.1.1.0^{5,6}]tricyclohexane are hydrogenolyzed simultaneously, since the logical intermediate (IV) and (V) are stable to reaction conditions. Meinwald²⁰ has observed similar results



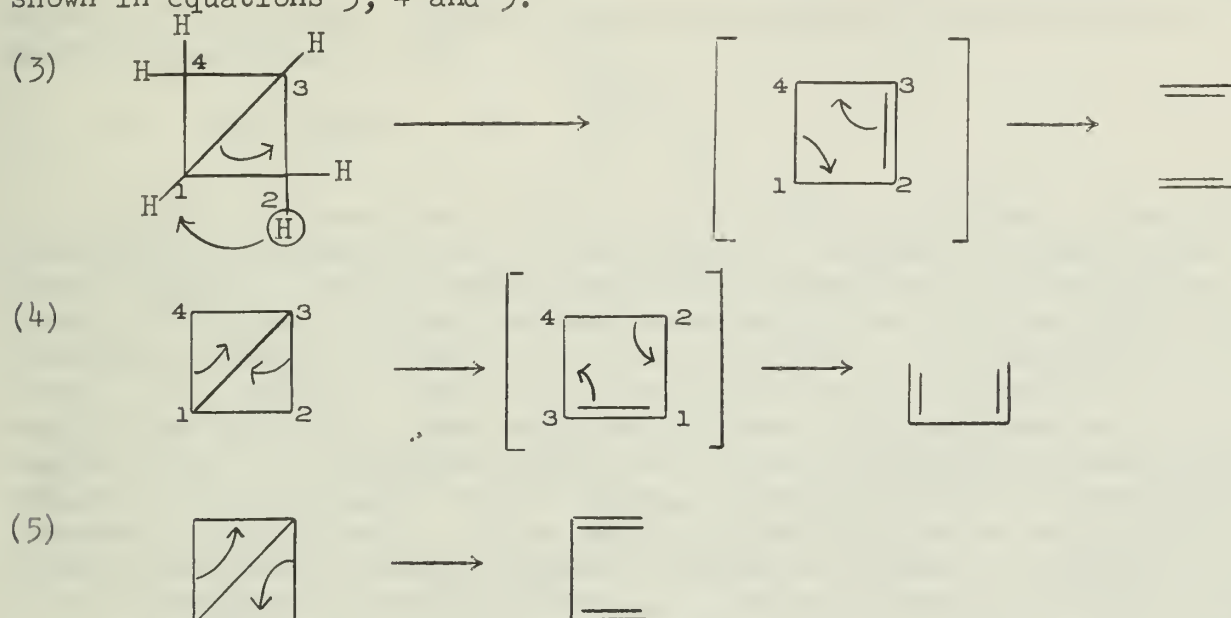
with tricyclo[2.1.1.0^{5,6}]hexane-5-t-butylcarboxamide, arguing that since none of the dihydro product could be recovered, the hydrogenolysis must occur simultaneously or in rapid succession. Hydrogenation of unbridged bicyclobutanes appears to proceed in a step-wise process. Griffin²⁴ and Doering¹⁰ have both isolated cyclobutanes from hydrogenation studies of bicyclic compounds. Both workers found the monocyclic compound to be that arising from cleavage of the 1,3-carbon-hydrogen bond. If the hydrogenation of tricyclo compounds does occur in a step-wise process, the intermediate arising from the absorption of one mole of hydrogen would probably be a strained bicyclo-compound which could readily absorb a second mole of hydrogen to give the observed products. Hydrogenation of a bicyclic compound, however, does not result in as much release of strain, thus the dihydro products can be isolated.

The thermal isomerization of bicyclobutanes has been investigated by several workers. The initial studies were done by Lemal⁹ and co-workers, who observed that the only product of the pyrolysis of bicyclobutane was 1,3-butadiene. They observed this transformation to occur at temperatures below 150°C. Later workers however, found the isomerization to require a temperature of at least 175°. Frey²⁸ and Srinivasan²⁹ simultaneously published results of kinetic studies on the pyrolysis of bicyclobutane. Both found the reaction to obey first order kinetics in the range of temperatures studied. Using the Arrhenius relationship, they obtain activation energies of 40.6-0.1 kcal/mole and 41.0-2.5 kcal/mole, respectively. Frey contends that the reaction is a true unimolecular decomposition since he observes no catalysis when the surface to volume ratio was increased. Srinivasan, however, has observed an increase in the rate of almost two to one when he increased the surface volume ratio. It should be noted that Frey could obtain reproducible results only after the vessel had been properly aged, indicating operation of some surface effect. This reaction may not be a true unimolecular decomposition.

It is noteworthy that bicyclobutane is thermally more stable than cyclobutene, while the monocycle is surely less strained than the bicyclic compound. Since the rate of isomerization of cyclobutene to butadiene proceeds with a rate at least 400 times that of bicyclobutane,³⁰ the latter isomerization must involve a higher

free energy of activation, since the rate of reaction parallels ΔF^\ddagger . Frey points out that there is a considerably greater difference in geometry between bicyclobutane and butadiene compared between cyclobutene and butadiene. He proposes that the relative stability of bicyclobutane is due to this rather than to the difference in the strain of the two molecules.

There are three reasonable modes for thermal reorganization of I. These are shown in equations 3, 4 and 5.



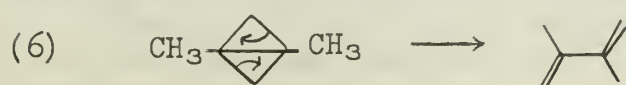
Frey excludes the first mechanism on the basis of energetic considerations, arguing that the observed energy of activation can not accommodate a carbon-hydrogen cleavage.

The second pathway, although it does not involve carbon-hydrogen cleavage may be disregarded since models show that the C_2 and C_4 carbon atoms lie in a plane perpendicular to the C_1 and C_3 carbons. For this mechanism to be operative, a tremendous distortion of the molecule would have to occur in the transition state. The observed energy of activation does not justify such a distortion. This argument should, however, be considered carefully, since there is no way of estimating the amount of strain in the activated complex.

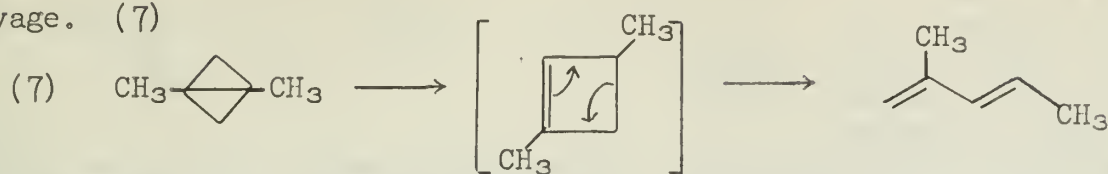
Srinivasan argues that the transition states of the cyclobutene pyrolysis and the bicyclobutane isomerization bear very little resemblance to each other. It has been experimentally determined that the frequency factor for the thermal isomerization of bicyclobutane to butadiene differs from the frequency factor for the isomerization of cyclobutene by a factor of at least $10^{28,30}$. Since one can write the Arrhenius equation as $k = (eKT/h) \exp(\Delta S^\ddagger/R) \exp(-E_a/RT)$,³¹ a correlation between the entropies of activation and the frequency factor can be made, if the frequency factors are measured at the same temperatures. Since both of these isomerizations are unimolecular, the difference in the entropy of activation is directly responsible for a change in the frequency factor. A difference of about 5 e.u. can be associated with a change in frequency factor of 10. Such a large difference in the entropies of activation suggests that the respective transition states have little in common, since the absolute entropies of the molecules differs by a factor of only 0.52 e.u.

The mechanism which both groups propose is a concerted cleavage of the 1,2 and 3,4 bonds (equation 5). Frey contends that the observed energy of activation is reasonable if one considers that the butadiene formed is in the somewhat strained cis configuration.

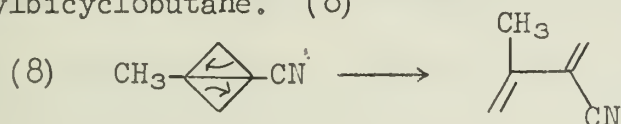
Chesick and coworkers have investigated the pyrolysis of 1,3-dimethylbicyclobutane.³² They conclude that the isomerization must proceed by concerted ring openings of the cyclopropane rings, since this rational readily explains the observed products. (6)



They observe no 1,3-dimethylbutadiene which would necessarily arise from 1,3-bond cleavage. (7)



Blanchard²¹ has found similar results on studies of the pyrolysis of 1-cyano-3-methylbicyclobutane. (8)

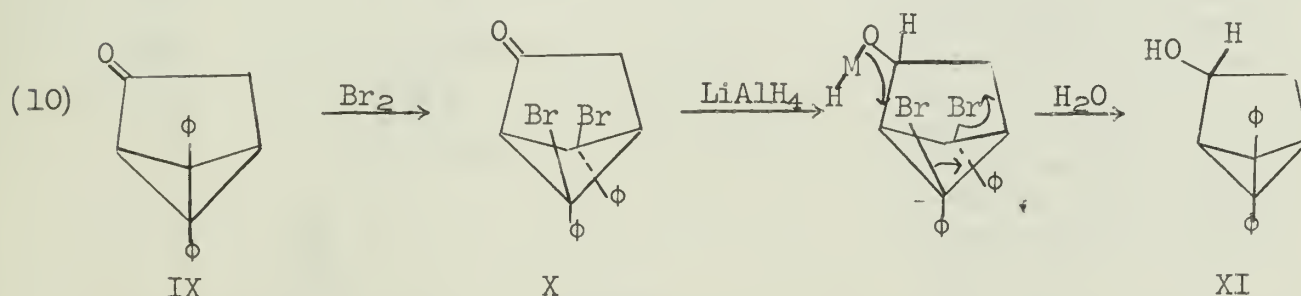
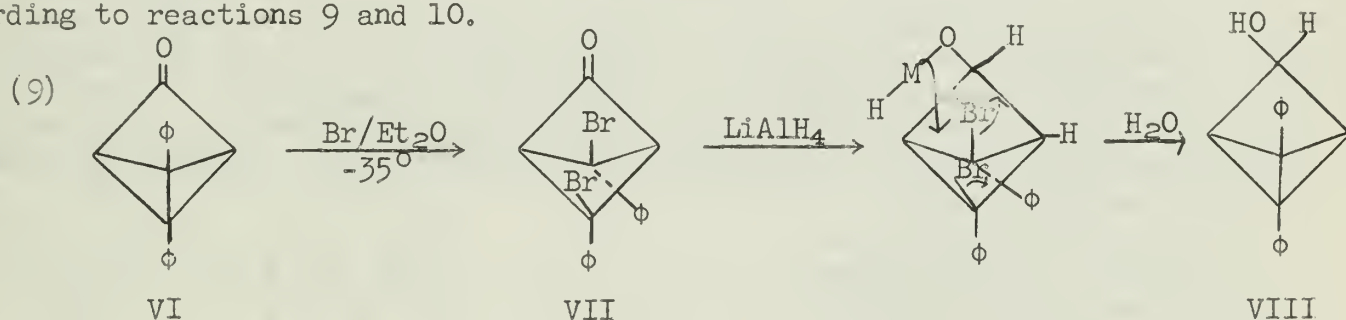


Chesick has found the activation energy for the thermal isomerization of 1,3-dimethylbicyclobutane to be 43.3 kcal/mole. Doering²⁶ contends this to be a concerted process. If one assumes that the minimum activation energy for a two step process is one which first involves breaking of the 1,2-carbon bond, the minimum activation energy is found to be 39.1 kcal/mole. (79, strength of 1^o-3^o carbon bond - 39.9, strain). Thus the observed activation energy is 4.2

kcal/mole larger than this estimated minimum. This difference is considerably smaller than the comparable difference in the cis-trans-interconversions of cyclopropane (11.3 kcal/mole) and the thermal isomerization of 2-methylbicyclo[2.1.0]pentane (9.7 kcal/mole). This small relative difference in the minimum and observed activation energy suggests a stepwise process is probably not operative here. Consequently, Doering proposes a concerted process for this isomerization.

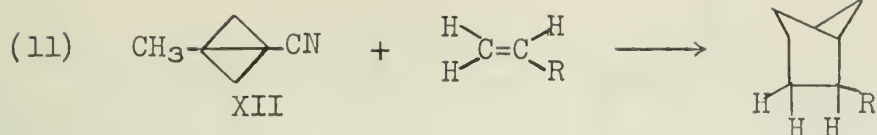
The strain in bicyclobutanes is reflected in the many facile addition reactions these compounds undergo. This reactivity is not entirely unexpected in view of the fact that the central carbon-carbon bond energy has become too low that the compound has acquired "pseudo-olefinic" character. Thus, it readily adds iodine to give a cis-trans mixture of diiodocyclobutanes.¹⁹ This reaction has been found to be reversible with sodium hydride. Similar reactions have been reported for 1,3-dimethylbicyclobutane,¹⁰ 1,3-trifluoromethyl-2,2,4,4-tetrafluorobicyclobutane,⁸ and the 1-cyano-3-methyl derivative.²¹

Masamune¹⁵ has reported that bromine readily adds to 4,5-diphenyltricyclo[1.1.1.0^{4,5}]pentanone-2 (VI), and to 4,5-diphenyltricyclo[2.1.1.0^{5,6}]hexanone-2 (VII) according to reactions 9 and 10.



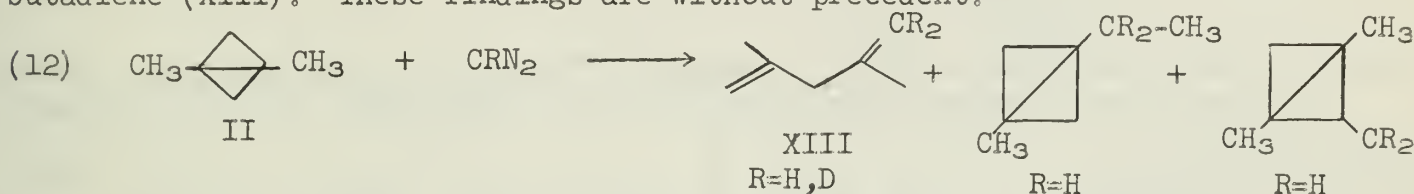
Compound (XI) is identical to that obtained by permitting (IX) to react with lithium aluminium hydride. The formation of (VIII) is given as evidence for the intermediacy of the unstable dibromide (VII).

Blanchard²¹ has recently reported that 1-cyano-3-methylbicyclobutane (XII) undergoes addition reactions with olefins. This reaction clearly demonstrates the reactivity of the C₁-C₃ bond.

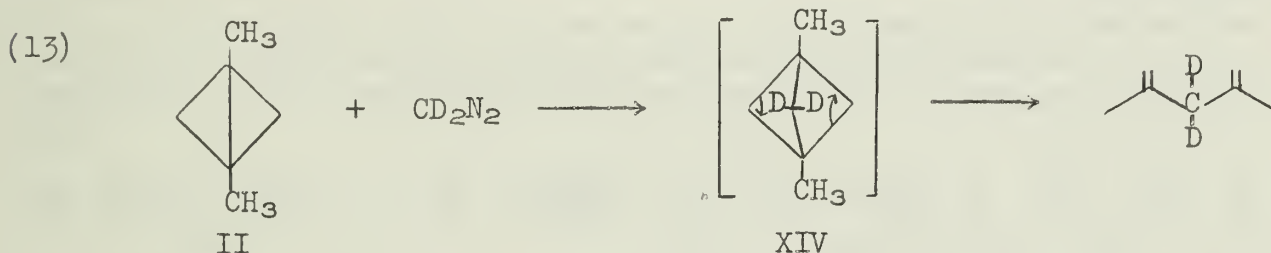


Doering and coworkers¹⁰ have treated 1,3-dimethylbicyclobutane (II) with diazomethane generated photolytically, and found that the

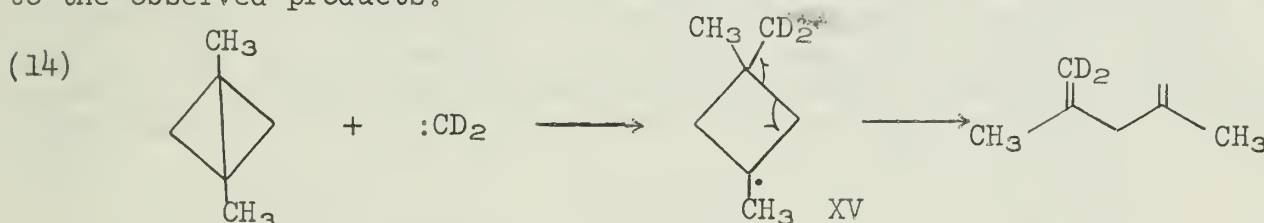
addition occurs in an unparalleled manner. On reaction with dideuteriodiazomethane, they observe exclusive incorporation of deuterium into the terminal methylene of the butadiene (XIII). These findings are without precedent.



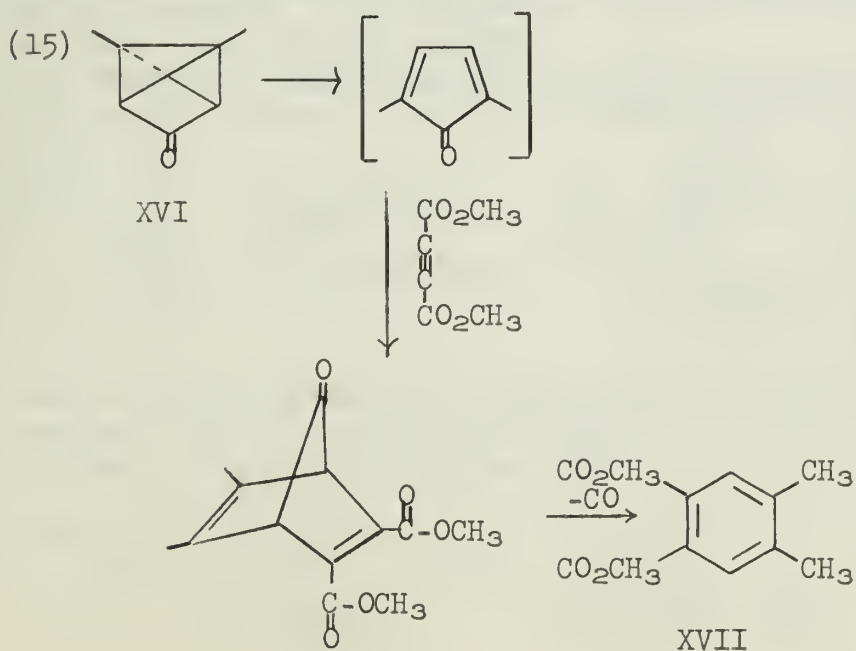
These workers argue that these results are not consistent with a tricyclopentane intermediate (XIV), since, in view of the symmetry of the transition state, some deuterium would be incorporated into the bis allylic - methylene position.



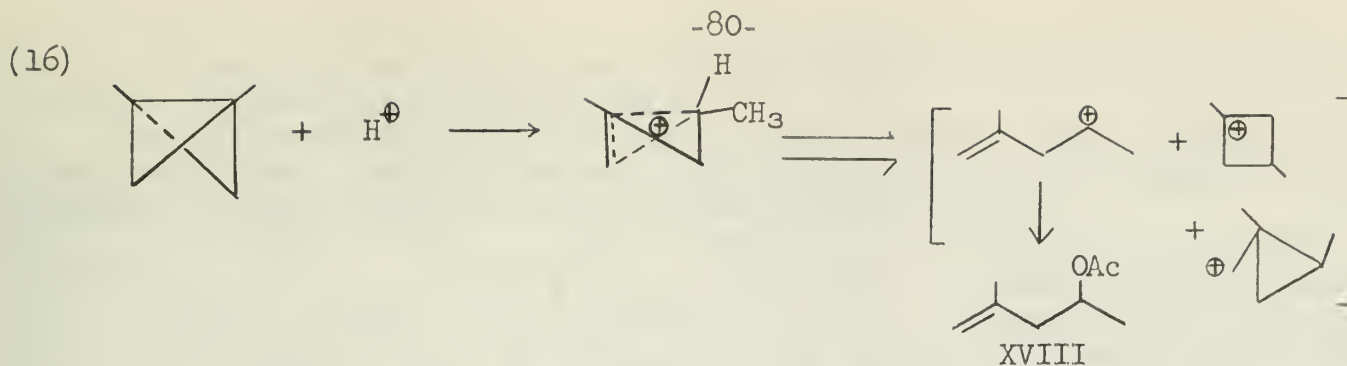
To explain the absence of deuterium in the non-olefinic position, they propose an unsymmetrical attack of the methylene to give a 1,4-diradical, (XV) which then cleaves to the observed products.



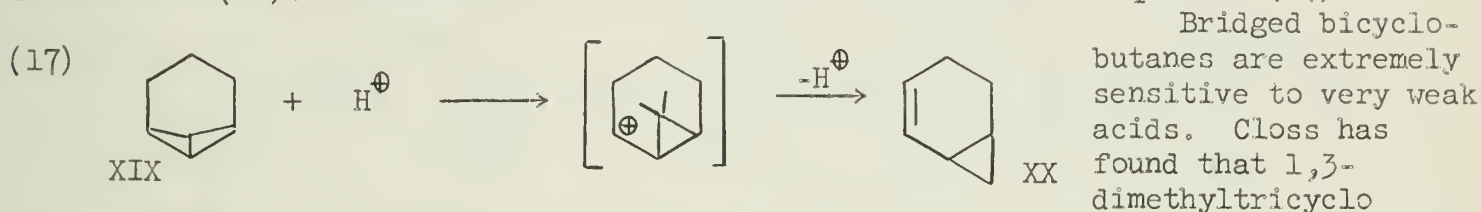
A Diels Alder reaction has been reported for a bridged-bicyclobutane,¹¹ however, the products can only be easily rationalized, assuming prior rearrangement of the bicyclobutane. 2,4-Dimethyltricyclo[1.1.1.0^{2,4}]pentan-5-one (XVI) when reacted with dimethylacetylenedicarboxylate affords 4,5-dimethylphthalate (XVII) and an unidentified product. The following equations show a probable reaction sequence.



Bicyclobutanes are very sensitive to acids, again reflecting the "pseudo-olefinic" character of the central bond. Doering¹⁰ has found that treatment of 1,3-dimethylbicyclobutane with acid leads to 2-acetoxy-4-methylpentene (XVIII), in addition to a minor unidentified product. He assumes the formation of a bicyclobutonium cation, contending that the presence of a second methyl group leads to more contribution from the allyl carbonyl moiety, and therefore a higher yield of the alkyl-carbonylacetate.



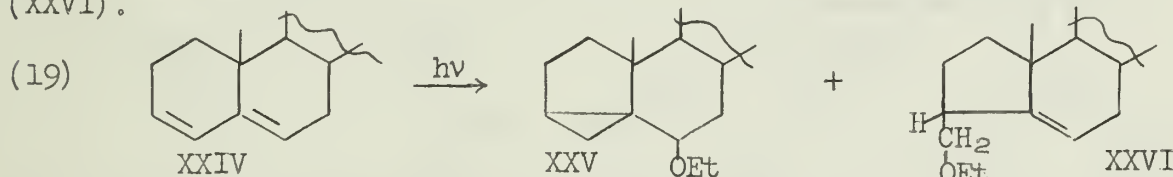
Moore⁷ has found tricyclo[3.1.1.0^{4,5}]heptane, (XIX) on treatment with acid, gives 2-norcarene (XX). This result can be rationalized as shown in equation (17).



[1.1.1.0^{4,5}] pentane (XXI) will rearrange at 2,5-dimethylcyclopentadiene (XXII) and 2,4-dimethylcyclopentadiene (XXIII), on treatment with methanol and water. The products may arise from initial protonation at the 4 position followed by rearrangement.

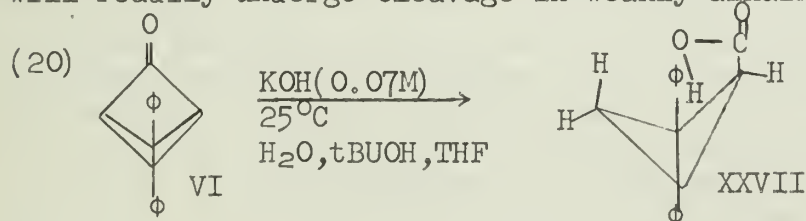


Dauben²⁴ has proposed a bicyclobutane intermediate to rationalize products obtained from the irradiation of steroids containing a transoid diene. He claims to have isolated the intermediate, although no compelling evidence for the structure is presented. He finds that in solvents such as water or ethanol, $\Delta^{3,5}$ -cholestadiene (XXIV) undergoes 1,3-addition of protic solvents upon irradiation to yield (XXV) and (XXVI).



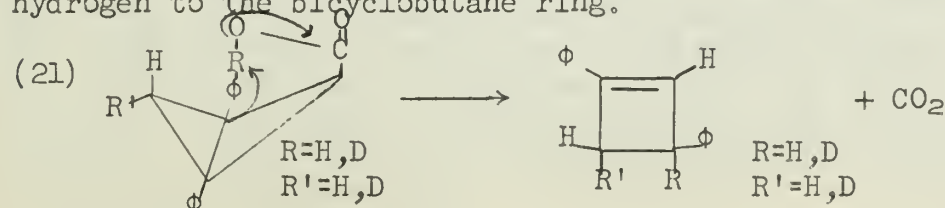
The extreme sensitivity of the compound to acid is thought to be a reflection of the very strained conformation of the bicyclobutane ring in the steroid. The instability of this compound in the presence of protic solvents is consistent with observations in known bicyclobutane systems.

Masamune¹⁵ has found that 4,5-diphenyltricyclo[1.1.1.0^{4,5}]pentanone-2 (VI) will readily undergo cleavage in weakly alkaline solution to give an acid (XXVII).



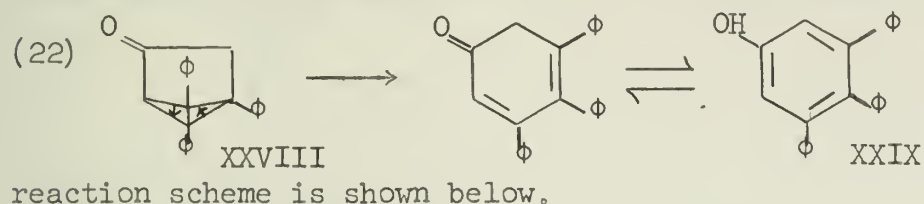
Since non-enolizable ketones generally require drastic conditions for cleavage, Masamune attributes the facile cleavage of (II) to the strain inherent in the molecule. The acid (XXVII) is interesting in view of the fact

that it readily undergoes decarboxylation to give cyclobutene derivatives. He contends that the rapid decarboxylation is due to the proximity of the acidic hydrogen to the bicyclobutane ring.

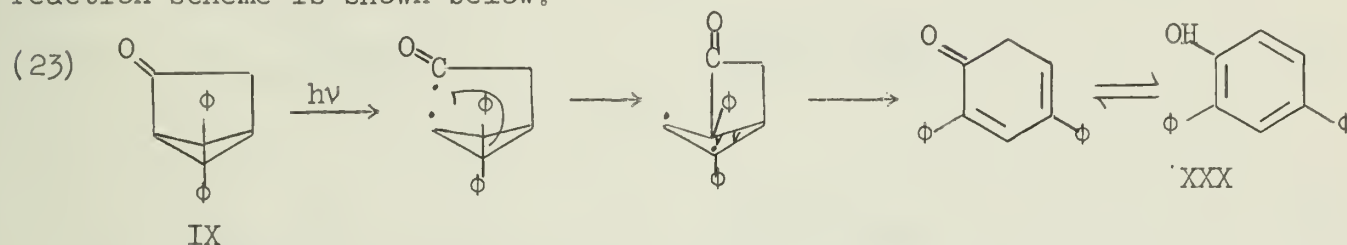


He has observed the exo-acid to be stable to similar decarboxylation conditions, which is consistent with this mechanism.

Some photoisomerizations of these compounds has been made, although they are poorly understood. Small¹² observed that irradiation of 4,5,6-triphenyl[2.1.1.0^{5,6}]hexanone-2 (XXVIII) provides 3,4,5-triphenyl phenol. (XXIX)

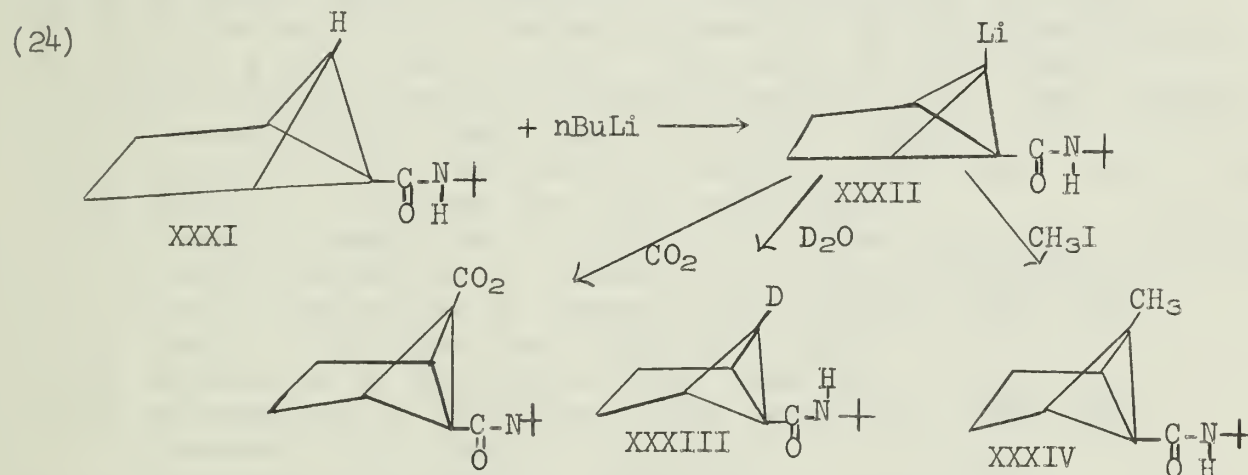


Masamune has reported 5,6-diphenyltricyclo[2.1.1.0]hexanone-2 is converted to 2,4-diphenylphenol (XXX) on photolysis. A possible



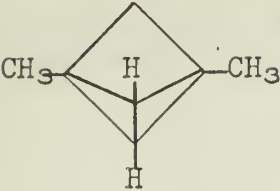


The skeletal structure of bicyclobutanes requires the bonding orbitals to be considerably distorted from 109°28'. The bond angle compression should be reflected in increased "p" character of the bonds in the ring and a corresponding increase in the "s" character of the exocyclic orbital. The acidic nature of the bridgehead hydrogens lends credence to this hypothesis. The acidity must be attributed to an increase in the amount of "s" character, since there is no easy way to delocalize the negative charge in the resulting anion.

Meinwald²⁰ and coworkers have carried out a number of reactions which demonstrate the acidic nature of the bridgehead hydrogens.



Closs¹⁶ has carried out similar reactions of the tricyclo[3.1.1.0^{6,7}]heptane, tricyclo[2.1.1.0^{5,6}]hexane, and tricyclo[1.1.1.0^{4,5}]pentane series. C¹³-H coupling has been used as a measure of the amount of "s" character in the carbon-hydrogen bond.³³ Some workers in this field have utilized this technique for estimating the amount of "s" character in the carbon-hydrogen bonds of bicyclobutane systems. Studies of the parent compound show the J_{C13-H} to be 159±2 cps and 170±2 cps for the methylene and bridgehead hydrogens respectively. Using the empirical correlation % "s" = 0.2 x J_{C13-H},³³ one arrives at the values of 32% and 34% "s" character for the methylene and bridgehead hydrogens respectively.

Bridging the ring should lead to considerable deformation of the orbitals and a corresponding increase in the "s" character of the bridgehead carbon-hydrogen bond. Closs has studied the tricyclo series,^{16,32} and attempted to correlate the relative rates of metalation using methyl lithium with the J_{C13-H}. He finds the expected increase in coupling constant with decrease in ring size. He also obtains a rough linear relationship between the rate of metalation and coupling constant. The results of his investigations are shown below. Infrared spectra of these compounds are also consistent with a carbon-hydrogen bond containing considerable "s" character.

Compound	$J_{C^{13}-H}$	k/k_o
	212 ± 0.5 cps	1.8
	206 ± 1 cps	1.1
	200 ± 1 cps	0.0

In summary, the reactions of bicyclobutane can be readily ascribed to the internal strain in these molecules. Further study of these and related compounds will result in an increased understanding of hybridization and the role of strain in defining the properties of cyclic compounds.

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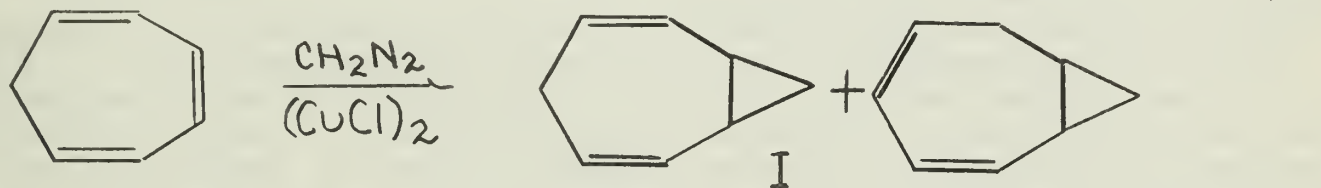
Reported by Martin Dines
INTRODUCTION

July 30, 1965

In the summer of 1963, J.C. Gaal of the University of Illinois presented a seminar on recent aspects of the Cope Rearrangement.¹ One of his principle objectives was to survey the recently investigated degenerate Cope Rearrangement, in which the structure of the product of the reaction is precisely that of the reactant. W. von E. Doering, who with Roth at Yale pioneered in this field, designated compounds which undergo such reactions "fluctuational structure" types. "Valence tautomerism" is another descriptive term frequently applied to these systems.

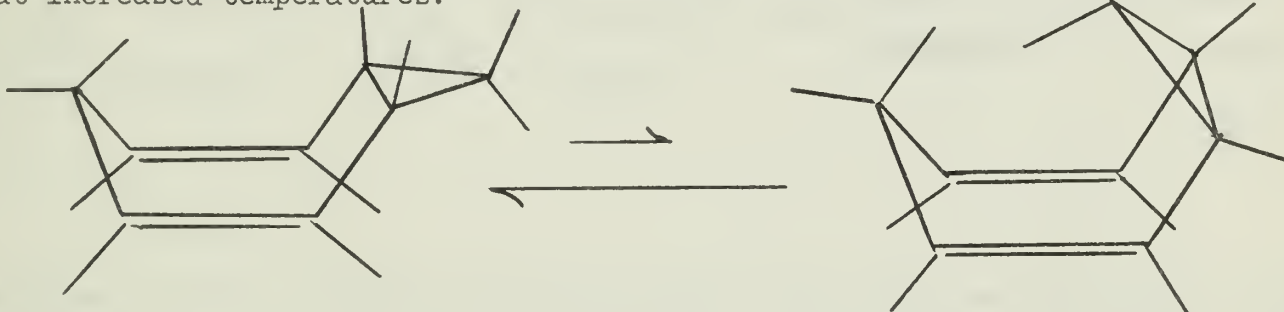
BACKGROUND

In 1962, Doering and Roth prepared 3,4-homotropilidene by the following straight-forward synthesis:

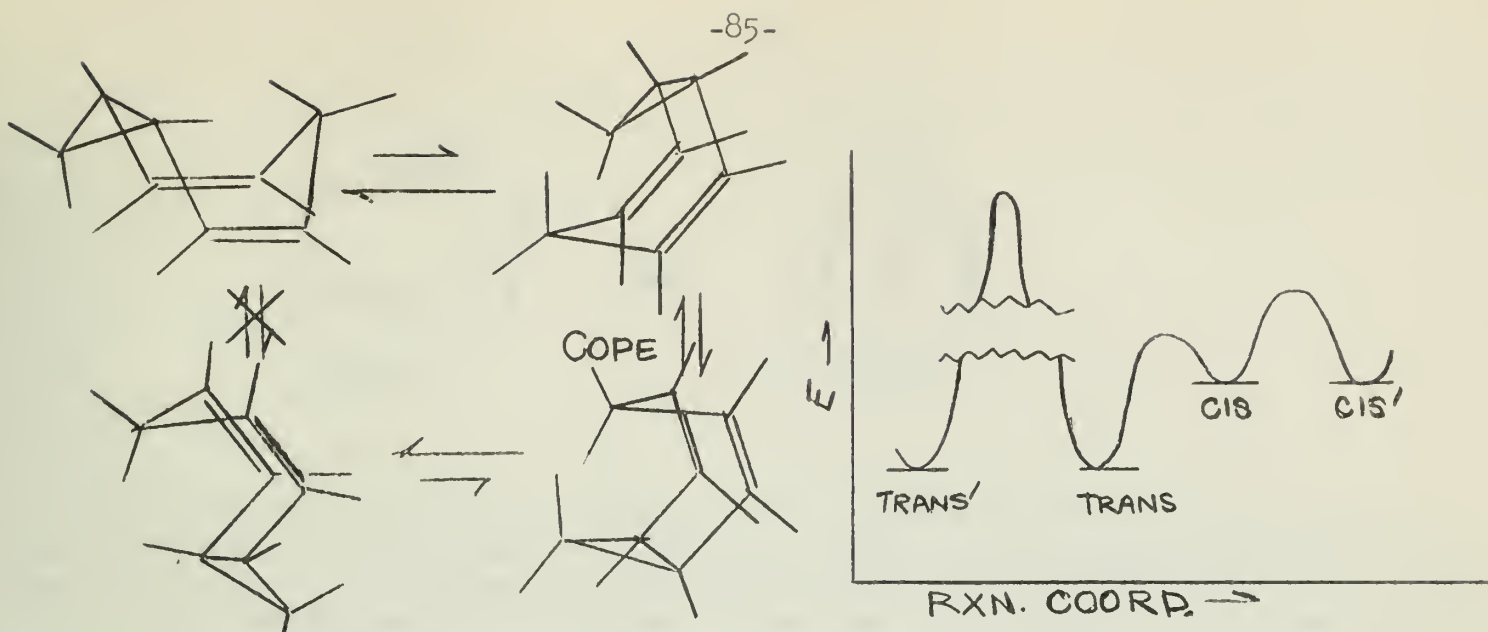


The two isomers were separated by gas-liquid partition chromatography and examined by the conventional spectral means.

The n.m.r. spectrum of I was found to be temperature dependent. This phenomenon can be rationalized by invoking the usual thermodynamic equilibrium situation in which a transoid and cisoid form of I are in equilibrium, with the less stable cis form preponderant at low temperatures, and the thermodynamically more stable trans form predominating at increased temperatures.

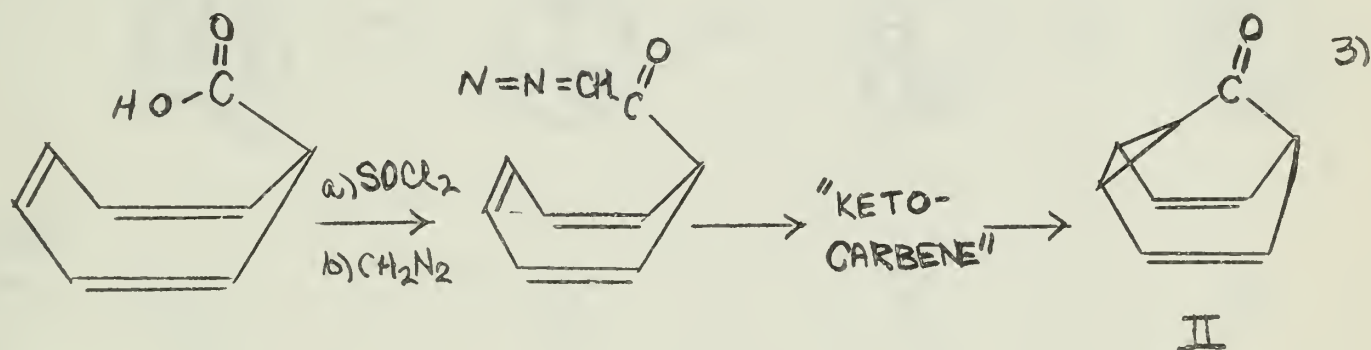


However, Doering found that the infrared spectrum of I taken over the same range of temperature as the n.m.r. showed no corresponding variation. He surmised that "the instantaneous structure of the molecule is independent of temperature within the range 20-185° C..." and that "...at all temperatures the observed N.M.R. and I.R. spectra pertain to the same molecule."² He reasoned that the transoid form of I is probably the preponderant isomer at all temperatures (due to an unfavorable trans-annular non-bonded hydrogen atom repulsion in the cisoid form), but that the molecule undergoes Cope Rearrangement through the cisoid isomer, presumably because of dihedral angle requirements between initial and final states of the rearranging molecule. The proposal can be summarized according to the following scheme:



Using chemical shift n.m.r. data, Doering estimated the rate of the degenerate rearrangement is of the order of 1000/second at 180°C, and about 1/second at -50°C.^{2,3}

Since the rearrangement could ostensibly occur only through a cisoid isomer, Doering suggested that if a bridge could be introduced across the ring such as to lock the 3,4-homotropilidene in the preferred cis conformation, a considerable rate enhancement might be observed. He further proposed a method of synthesizing a 3,4-homotropilidene with a carbonyl bridge. As a precursor he employed tropilidene carboxylic acid.



The resulting "locked" cisoid 3,4-homotropilidene derivative was christened "barbaralone", and a study of its rate of "self interconversion" was carried out by Lambert using the method of Anbar for n.m.r. line width data. Rates were calculated from the formula

$$R_t = \frac{\pi}{2} \frac{\delta^2}{\Delta - \delta_0} \quad \text{in which } \delta \text{ represents the difference in chemical shifts}$$

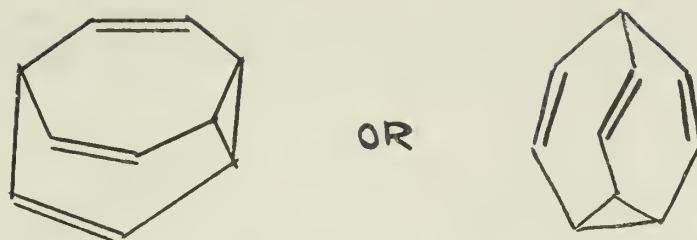
at temperature t , Δ the line width at half height, and δ_0 the natural line width. Some of Lambert's results are:

Temp: (°C)	R (sec ⁻¹)
-31°	8190
-41°	3500
-48°	2260
-55°	1200

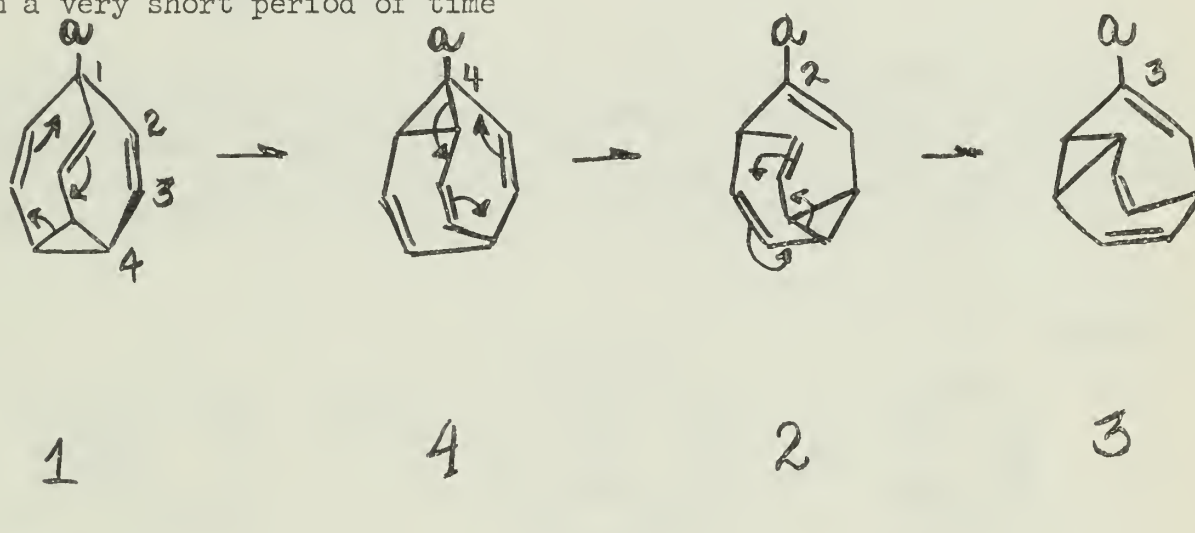
4)

$$E_{\text{act}} = 8.1 \text{ kcal/mol}$$

It occurred to Doering that the ultimate fluconal-structure system might be achieved by a molecule he postulated in which 3,4-homotropilidene is locked in a cisoid configuration by a vinyl bridge. The vinyl bridge would not only function to lock I in the favorable cisoid isomer, but also would provide numerous alternate pathways for the isomerization reaction.^{2,3} His colleagues affectionately named the molecule "bullvalene" in honor of Professor Doering.



Potentially the most interesting feature of Professor Doering's hypothetical bullvalene could be the ability to effectively (for an n.m.r. instrument) render its four chemically non-equivalent protons magnetically indistinguishable (providing that the rate of rearrangement is much greater than the rate of the n.m.r. relaxation time). To visualize how bullvalene might achieve this unique scrambling, label the proton initially at the bridgehead "a". Then, label the four chemically different positions 1, 2, 3, and 4. It can be shown that three properly chosen Cope rearrangements can cause the chemical environment of proton "a" to change to that of hydrogens 1, 2, 3, and 4 presumably in a very short period of time



Doering predicted that bullvalene would probably show a complex four-signal spectrum in the n.m.r. at low temperatures, which would collapse upon increased temperature until the point was reached at which a single sharp signal would appear, representing all ten of bullvalene's four different protons. Simple permutation and symmetry calculations show that there are 1,209,600 possible structures for bullvalene, assuming distinguishable carbon atoms.

Assuming that bullvalene rearranges at a rate corresponding to that of barbaralene, it might seem that the coveted distinction between mesomerism and tautomerism would shrink into ambiguity. (i.e. vs. 1.2 million rapidly interconverting tautomers).

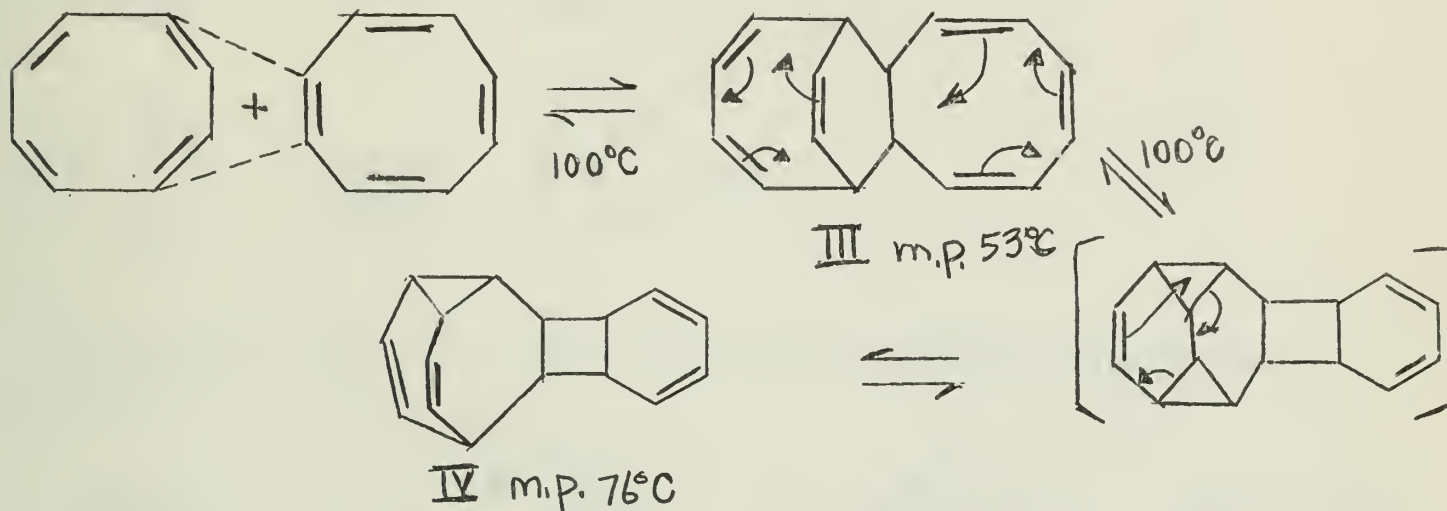


Such confusion may be avoided if it is recognized that it is geometrically impossible to arrange ten points on the surface of a sphere to form a completely symmetrical three-dimensional figure. This limitation precludes the application of the resonance concept, hence we must unequivocally be dealing with an example of tautomerism.³

SYNTHESIS OF BULLVALENE

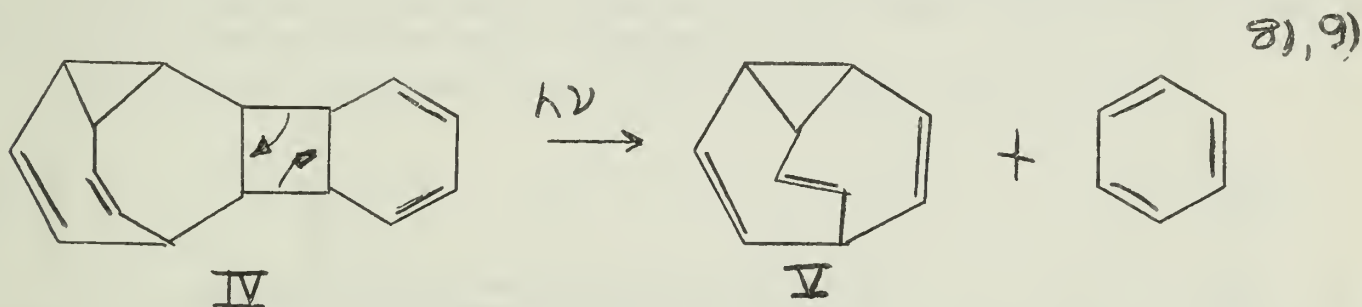
In 1963, Gerhard Schroeder in Belgium was working on the base catalysed dimerization

of cyclooctatetraene. W. O. Jones had reported in 1955 that two isomers of the dimer were formed under the reaction conditions, one with a melting point of 53°C , the other at 76°C , but Jones failed to correctly assign structures to the isomers.⁵ Schroeder further investigated the reaction and characterized the dimers.^{6,7}



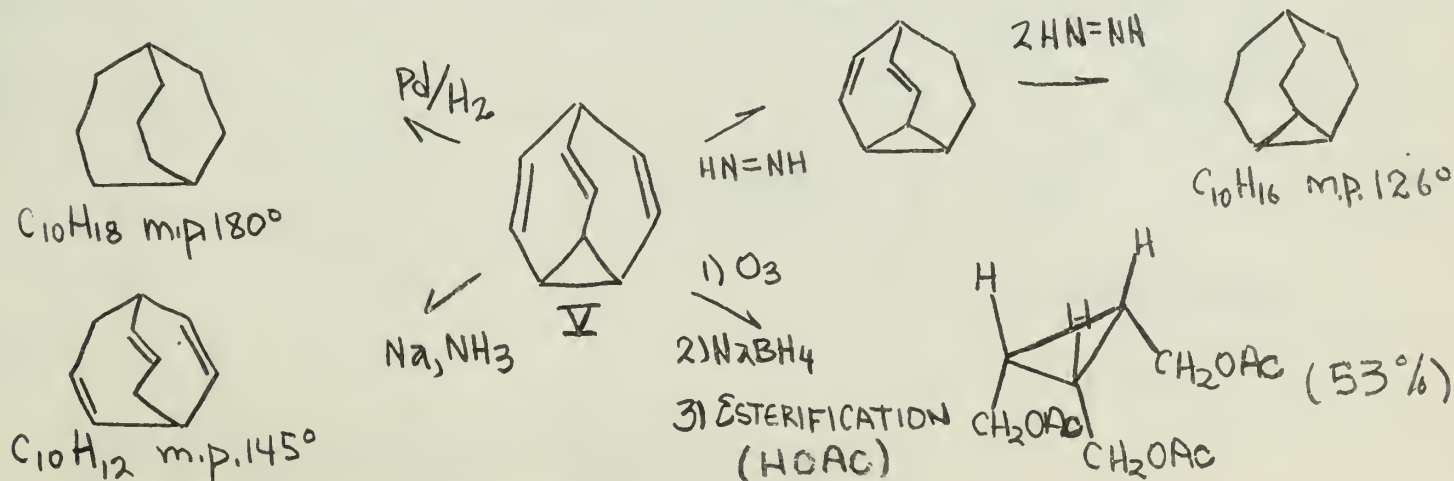
Schroeder noticed that the structure of the 76°C melting isomer incorporated the 3,4-homotropilidene system in a suggestive manner. Furthermore, IV exhibited n.m.r. properties similar to those of barbaralene — namely a temperature dependent spectrum.⁶

Within a year after Doering conceived of bullvalene, Schroeder irradiated IV and obtained tricyclo(3.3.2.0^{4,6})deca-2,7,9-triene, or bullvalene, in an 80% yield.

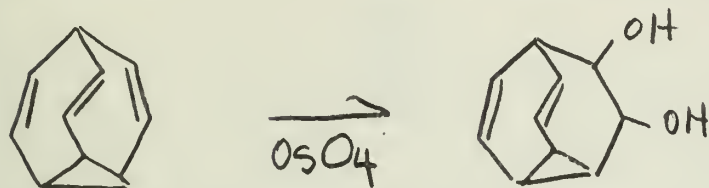
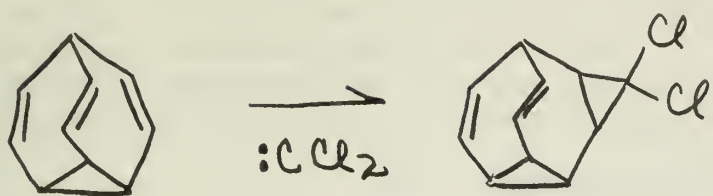


Bullvalene melts at 96°C and sublimes readily. Its ultraviolet spectrum shows an absorption at $238\text{ m}\mu$ ($\epsilon_{\text{max}} = 1700$). The infrared spectrum was temperature independent as expected.

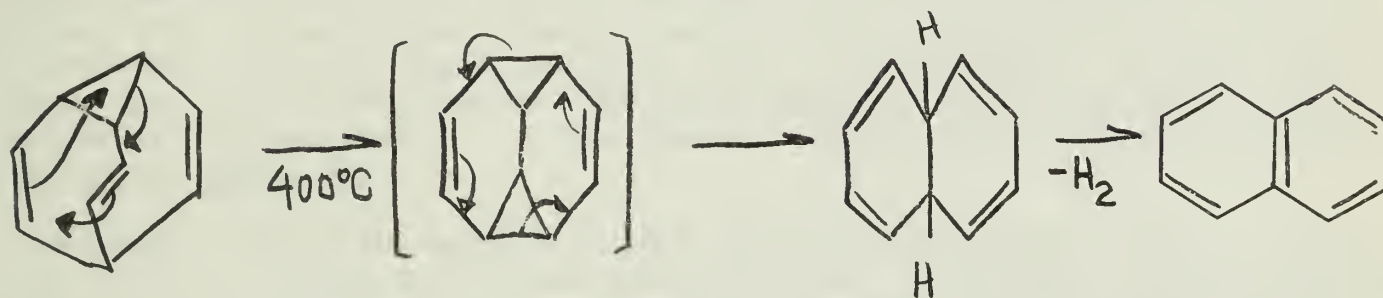
Conventional methods of reduction of one or more of the olefinic bonds and the cyclopropyl system of bullvalene was easily accomplished.



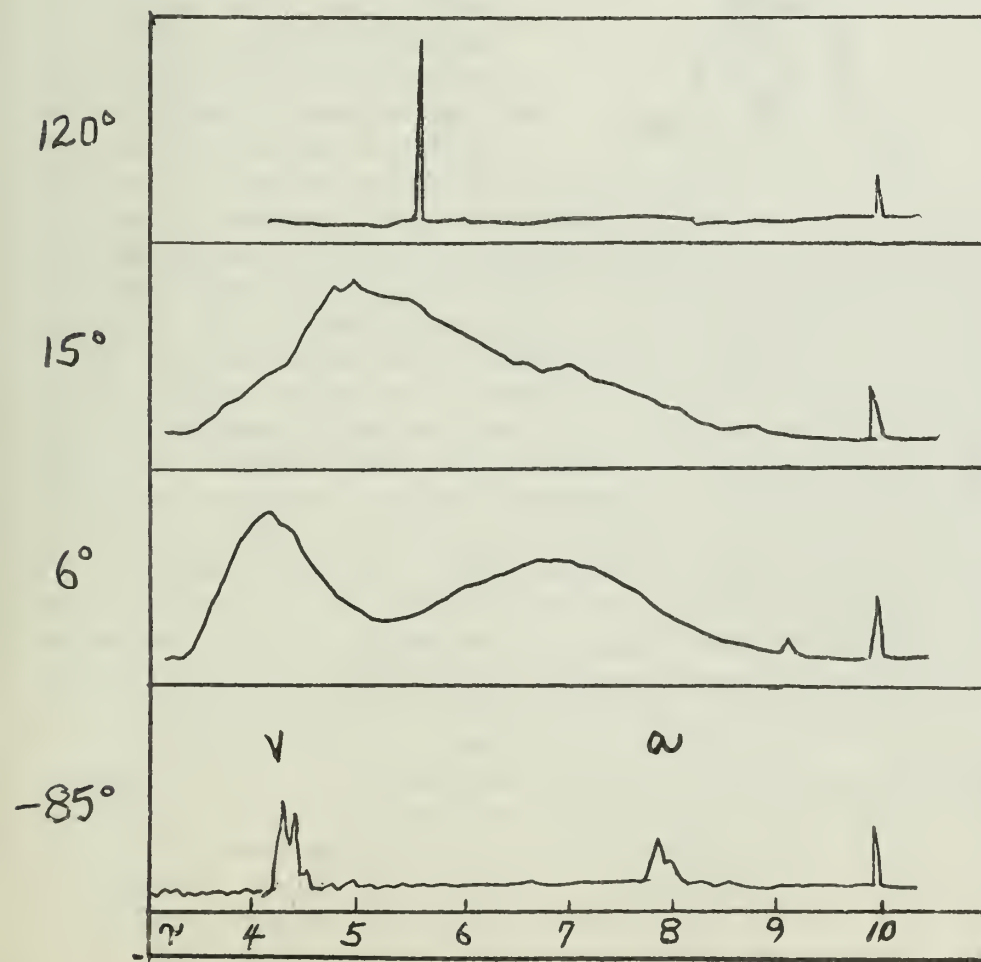
Bullvalene behaves like a typical olefin toward carbenes and oxidizing agents.



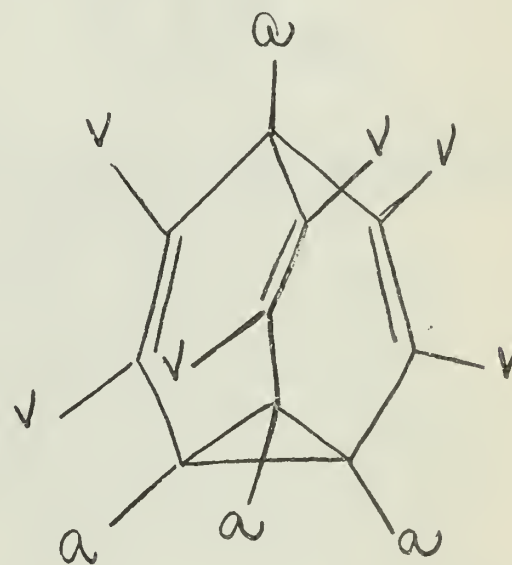
When heated to $400^\circ C$, bullvalene collapses and subsequently aromatizes to naphthalene.



Finally, the most interesting property of bullvalene, predicted by Professor Doering, and revealed by its n.m.r. spectrum, is the scrambling of its ten hydrogens which results from many fast self-interconversions.



10)



4 aliphatic
6 vinyl

The two multiplets in the n.m.r. spectrum of V taken at -85°C have area ratios of 6:4 and τ values of 4.35 and 7.92. If the single signal observed at 120°C is a true average of all of the protons, its τ value should fall at $\frac{6 \cdot 4.35 + 4 \cdot 7.92}{10} = 5.78$. The actual experimental value is τ 5.78.¹⁰

Saunders obtained rate data for the tautomerization of bullvalene using shapes of the peaks in the n.m.r. spectrum.¹¹ Some of his results are:

$^{\circ}\text{C}$	Line width in cps at half height	$k(\text{sec}^{-1})$
10.5	197	1200
33.6	41.7	6000
65.2	6.7	36000
82.7	3.1	79000

$$E_{\text{act}} = 11.8 \pm 1 \text{ kcal/mol}$$

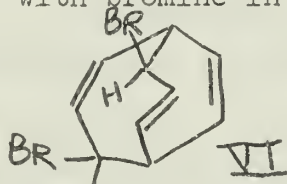
There is an apparent anomaly in the rate data, since Lambert's calculations on barbaralone indicated a rate of 8190 sec^{-1} at -31°C and an E_{act} of 8.1 kcal/mol . Intuitively, one would guess that bullvalene, having many more rearrangement possibilities than barbaralone, would proceed at a faster rate. However, it follows from the rate data that the transition state for the rearrangement of barbaralone lies relatively lower than that for bullvalene. Lambert suggests that this rate enhancement observed for II may arise from the inductive effect of the carbonyl group of barbaralone, or from the larger angle strain arising from the single carbon bridge.⁴ One effect involves a raising of the initial state, the other a lowering of the transition state.

DERIVATIVES OF BULLVALENE

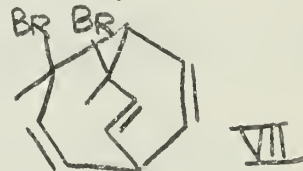
Bullvalene derivatives deserve special attention because they provide insight into the nature of bullvalene's fluxional structure. For example, a mono-substituted derivative should exhibit in the course of its rearrangements four different chemical compounds, having different ground state energies, and probably slightly different relative transition state energies.

Schroeder treated bullvalene with bromine in methylene chloride, and obtained a dibromide which was either

Its n.m.r. spectrum showed no temperature dependency, and further demonstrated that the bromine atoms occupied non-equivalent sites on the molecule.¹¹



or



(2)

Schroeder deduced that VI is the structure of the dibromide. It should be noted that one bromine atom occupies an axial position on one of the seven-membered rings, and the other an equatorial position on the other cycloheptadiene ring. Addition of potassium *t*-butoxide in *t*-butanol resulted in the formation of monobromobullvalene in a

70% yield, which had a temperature dependent n.m.r. spectrum. At 142°C a single sharp proton resonance signal was observed, which broadened on cooling. At -45°C two multiplets appeared, one at τ 7.6 (aliphatic protons) and one at τ 4.2 (olefinic protons). Their area ratios were 4:5 respectively, indicating that at -45°C the bromine occupies a vinylic position in the most stable tautomer. Reduction of monobromobullvalene with lithium in *t*-butanol regenerated the parent hydrocarbon, bullvalene.

t-Butylbullvalyl ether can be formed easily by the addition of alcohol-free potassium *t*-butoxide to either mono- or di-bromobullvalene in boiling petroleum ether. As expected, this compound has a temperature dependent n.m.r. spectrum, having two sharp peaks which are apparent at higher temperatures with an area ratio of 1:1, arising from nine bullvalene protons and the nine *t*-butyl protons.

At about -60°C , a multiplet appears at τ 4.35 (bullvalene olefinic protons), a doublet at τ 5.0 (bullvalene olefinic protons neighboring the *t*-butoxide group) and a multiplet at τ 7.90 (bullvalene aliphatic protons). The *t*-butoxy protons fall at τ 8.8. The area ratios of the three bullvalene signals were 4:1:4. As with monobromobullvalene, vinyl substitution is preferred in the most stable isomer. Schroeder concluded that in both monosubstituted derivatives, the preference for substitution on a vinyl position at low temperatures is greater than 80%.¹²

Oth and Merenyi calculated relative rates of rearrangement at 0° C for the derivatives on the basis of n.m.r. coalescence temperatures.¹²

Compound	k (sec ⁻¹)	E _{act} (kcal/mol)
Bullvalene	165	13.1
Bromobullvalene	88	12.8
<u>t</u> -Butylbullvalyl ether	62	12.5
Error	±.2	± 1

The E_{act} values as shown must be incorrect, since a slower rate corresponds to a higher E_{act}. Perhaps the values for bullvalene and t-butylbullvalyl ether are reversed. If this is correct the E_{act} would then correspond more closely to the value of 11.8^{±1} kcal/mol reported by Saunders.

CONCLUSION

Thus has bullvalene chemistry developed from an interesting conjecture to a reality. In their last communication, Schroeder and his group have expressed their intent to synthesize other derivatives to further understand the nature of the fluxional structure reaction, and especially to attempt to further elucidate the complex transition state situation.

Most interesting at this point in the development of the theory of the degenerate Cope Rearrangement would be a detailed molecular orbital treatment along the lines of the work of Hoffmann and Woodward at Harvard of the pi electron conditions both in the ground states and in the transition state.

To assist in the gathering of pertinent data for such a study and for any other work pertaining to bullvalene and the Cope Rearrangement many new derivatives of bullvalene must be developed, and a comprehensive search initiated for other compounds perhaps more involved than 3,4-homotropilidene or bullvalene which may undergo a valence isomerization.

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MECHANISMS OF ORGANIC HALIDE REDUCTION BY CHROMOUS ION

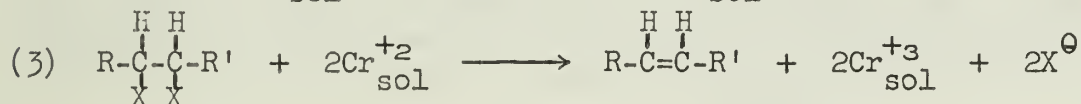
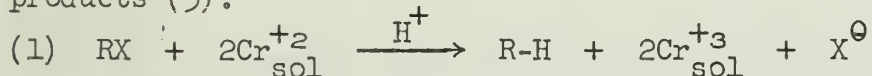
Reported by Steven Dombchik

August 2, 1965

INTRODUCTION

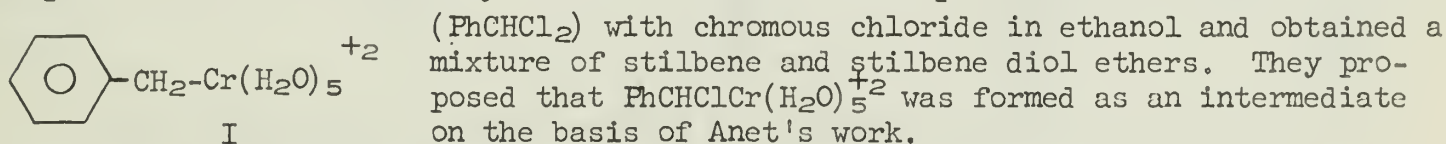
Chromium (II) salts are excellent reducing agents for a variety of organic compounds.^{1,2,3} The reduction generally involves the replacement of the functional group with hydrogen or addition of hydrogen across multiple bonds if present. Coupling and elimination products are also commonly observed. The synthetic uses of chromous ion as a reducing agent have received considerable attention particularly in the area of natural product chemistry. There has been a recent review covering this area.³ Although Berthelot⁴ first used chromous ion as a reducing agent in 1886, until recently very little work had been carried out with the objective of determining the mechanism of this reduction. It will be the object of this seminar to try to summarize the data bearing on the mechanism of Cr(II) reductions with respect to organic halides. Furthermore, the discussion will be limited mainly to the reduction of allylic, benzylic and related halides although references to other systems will be made when pertinent.

The effectiveness of chromous ion as a reducing agent for organic halides depends on the structural type as well as the halides employed.⁵ Generally the rates of reduction parallel solvolytic reactivity of the halide. There are two general reductions which an organic halide may undergo. There may be a reduction leading to alkane (1) or to dimeric product (2). Alkyl halides are reduced exclusively to alkanes. Allylic halides, benzylic halides, and α -halocarbonyl compounds may be reduced to either alkanes or dimeric products. The ultimate product ratio in the latter case is dependent upon reaction conditions, solvent, and halide used. With the specific cases of vic-dihalides and halohydrins olefins are the sole reduction products (3).

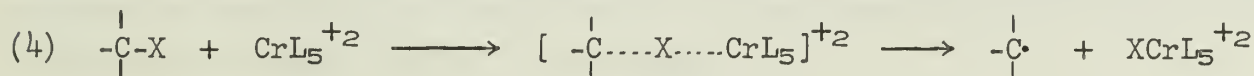


BENZYLCHROMIUM ION INTERMEDIATE

In general benzyl halides have been employed as substrates for the study of Cr(II) reductions because an observable intermediate is formed. It has been suggested that the reduction of all organic monohalides proceed by a common path.^{6,7,8} Anet and LeBlanc⁹ showed that when benzyl chloride is reduced by Cr(II) a mixture of toluene and bibenzyl is formed. They demonstrated that the initial reaction of benzyl chloride with chromous perchlorate produces a benzylchromium complex I which is relatively stable. Neumer and Aktipis¹⁰ reduced benzal chloride

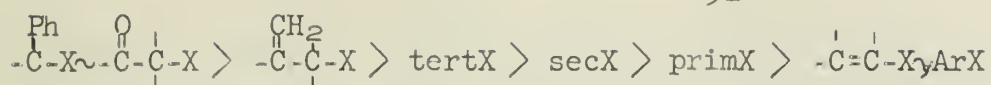


Castro and Kray¹¹ maintain that the rate determining step in the reduction of organic halides by chromous sulfate is the attack of the metal ion on the halide (4).



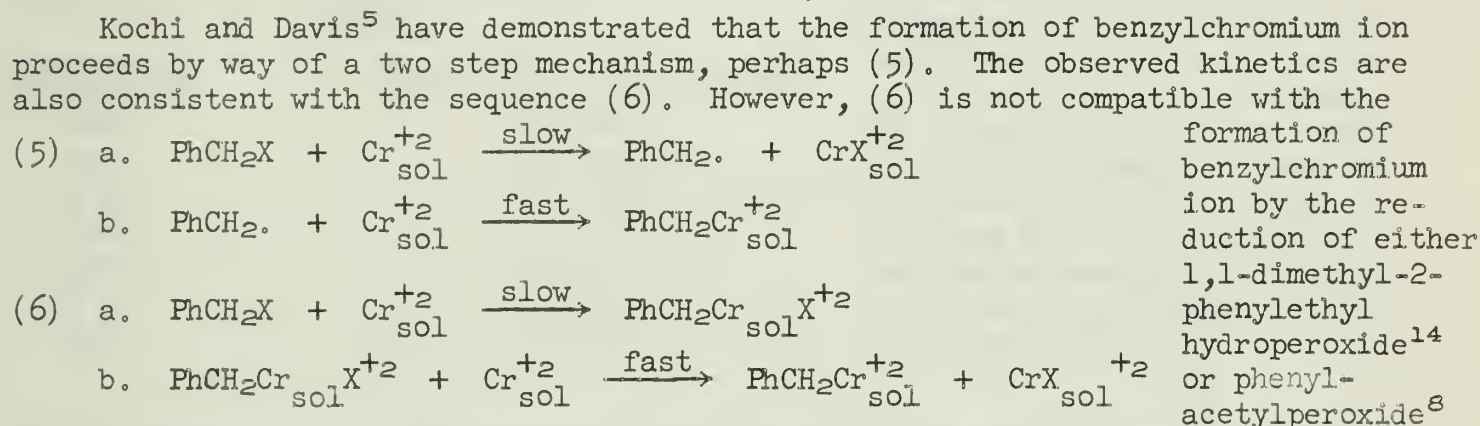
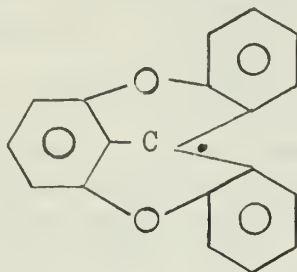
L=Ligand

This they suggest leads to the transfer of a halogen atom from the carbon atom to the chromium producing a free radical. The overall order of the reduction of allyl chloride by Cr(II) was found to be 1.98. Furthermore the inorganic ion resulting from the reduction of alkyl chloride is the apple-green CrCl⁺² and not the deeper green CrSO₄. The reactivity of monohalides with Cr(II) fall in the order:



This is consistent with participation of the organic halide in the

rate determining step. The initial step and transition state shown in (4) are entirely analogous to the processes described by Taube for the reduction of inorganic ions like $\text{Cr}(\text{NH}_3)_5\text{Cl}^{+2}$ and $\text{Co}(\text{NH}_3)_5\text{Cl}^{+2}$ by chromous ion.¹² The formation of II upon treatment of the corresponding halide with chromous chloride in acetic acid has been cited as evidence for the initial formation of a free radical.¹³



with Cr(II). The rate of appearance of benzylchromium ion followed spectrophotometrically is found to have the same rate constant as the disappearance of benzyl chloride as determined by gas chromatography.

A final piece of evidence favoring homolytic dissociation of benzyl halides is that relative rates of dissociation of substituted benzyl bromides in pyrolysis reactions,¹⁵ a known homolytic process, and Cr(II) reductions are very similar with neither following the Hammett sigma relationship (Table I).

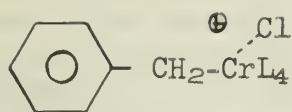
Table I

Relative Rates of Reduction and Pyrolysis of Benzyl Halides				
Rel. rates of benzyl halides reduction with Cr(II)		Rel. rates pyrolysis	Hammett σ	Substituent
Bromide	Chloride			
1.00		1.00	0.000	H
1.04	(1.02)	1.02	-0.069	<u>m</u> -Me
1.33		-----	-0.170	<u>p</u> -Me
1.07		1.13	0.373	<u>m</u> -Cl
	(1.26)	1.30	0.227	<u>p</u> -Cl
1.17		1.24	0.391	<u>m</u> -Br
1.04		-----	0.115	<u>m</u> -MeO

The decomposition of benzylchromium ion leading to toluene and bibenzyl has been shown to proceed by independent routes.⁷ In the subsequent discussion the sequence of general reactions proposed for the formation of alkane or dimeric products through benzylchromium ion and other routes will be treated separately.

FORMATION OF ALKANE UPON Cr(II) REDUCTION

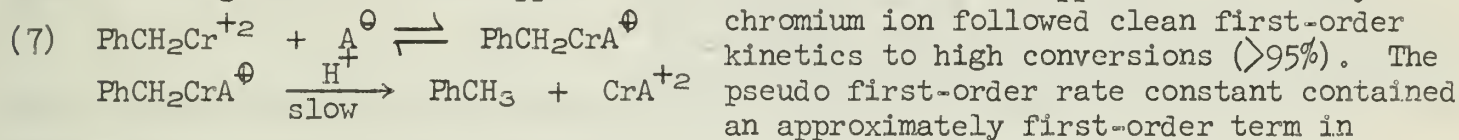
Anet and LeBlanc⁹ upon reducing benzyl chloride with chromous chloride in hydrochloric acid obtained only toluene and no intermediate was detected. It was postulated that in this case the initially formed complex was III and not the benzylchromium ion. Work by Taube and coworkers^{16,17} with analogous inorganic systems indicate that III, if formed, could lose a halogen by bridging with



III

another chromous ion and would no longer be as inert as I, but could dissociate to a benzyl anion. This anion would then certainly react with a hydrogen donor or hydronium ion to give toluene.

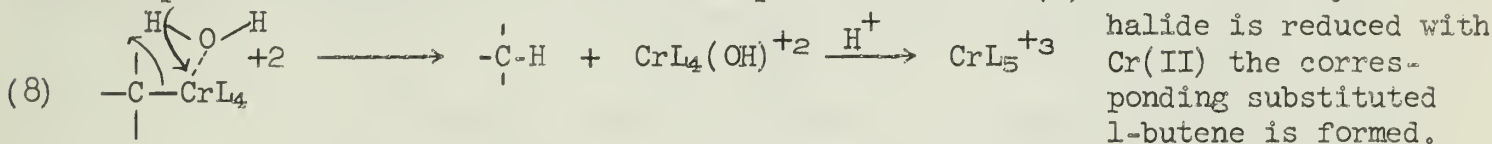
Kochi and Buchanan⁷ have reported that the protonation of benzylchromium ion to give alkane is general base and acid catalyzed and dependent on specific anion effects. They propose that the reaction occurs in two steps (7).



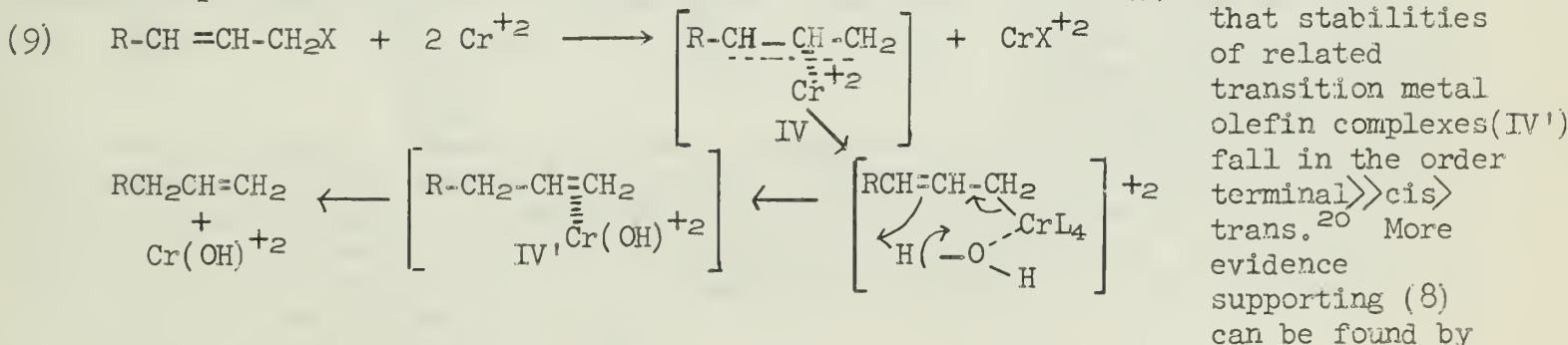
The following observations support this mechanism. The disappearance of benzylchromium ion followed clean first-order kinetics to high conversions (>95%). The pseudo first-order rate constant contained an approximately first-order term in

Table II		character on the benzylic system in the transition state during protonation. The authors suggest that the formation of the new carbon-hydrogen bond might precede the breaking of the old carbon-chromium bond. The data are perhaps accommodated better by a simultaneous breaking and formation of bonds.
Substituent	First-order rate constant	
none	1.01×10^{-2}	
m-Me	5.40×10^{-3}	
p-Br	4.49×10^{-3}	
p-Me	4.18×10^{-3}	
m-Br	3.35×10^{-3}	
m-Cl	2.68×10^{-3}	
o-Me	2.45×10^{-3}	

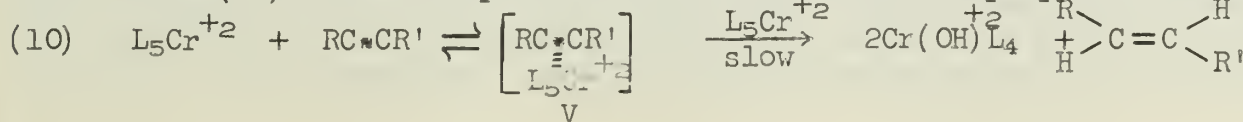
Castro and Kray¹¹ on the other hand have proposed that the reduction of alkyl halides to the corresponding alkanes through an RCrL_5^{+2} intermediate requires an initial heterolytic scission. They believe that this cleavage can best be described as a synchronous process in which a proton is transferred from the solvation sphere of the metal ion to the incipient carbanion (8).



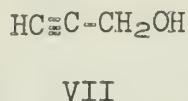
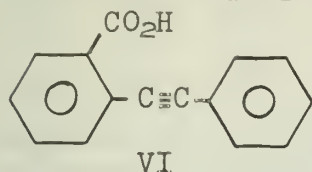
It is noteworthy that the equilibrium distribution of butenes at room temperature is 77% trans- and 21% cis-2-butene and only 2% 1-butene.¹⁹ The selectivity observed in the case of Cr(II) reductions can be rationalized by invoking a π -allyl chromic complex IV as an intermediate in the over all reduction (9). It is known



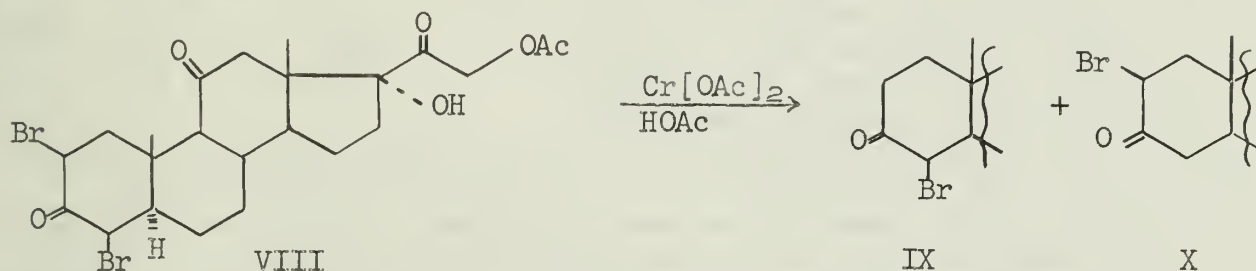
looking at the chromous ion reductions of acetylenes. Internal acetylenes are converted in a stereospecific manner to the corresponding trans olefin.²¹ A mechanism (10) consistent with experimental data favors the rapid and reversible formation of a 1:1 acetylene-chromous ion complex followed by a rate determining attack of Cr(II) on the complex V. The coordination step appears reasonable in view



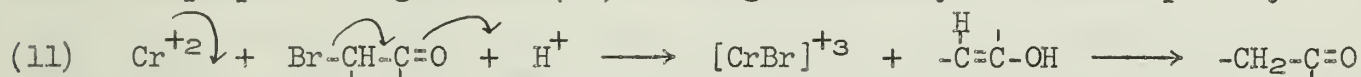
of the fact that *o*-carboxytolan(VI) is reduced by Cr(II) whereas the *para* isomer is not. The second chromium ion should be expected to approach the complex V from the least hindered side, i.e. that opposite the already bonded metal ion. Proton transfer in the rate determining step is supported by the observation that the reduction of propargyl alcohol (VII) proceeds 3.5 times faster in water than in D₂O.



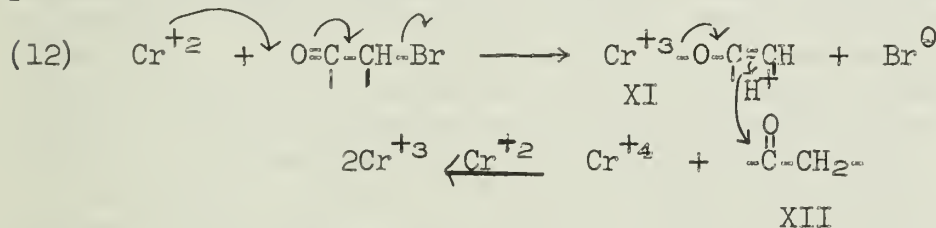
hydroxy-5 α -pregnane-3,11,20-trione (VIII). The major product is the 4 β -bromo isomer



IX with a small amount of the 2 β -bromo isomer X also being formed. The overall mechanism proposed is given in (11). Slauch and Raley⁵ converted phenacyl bromide

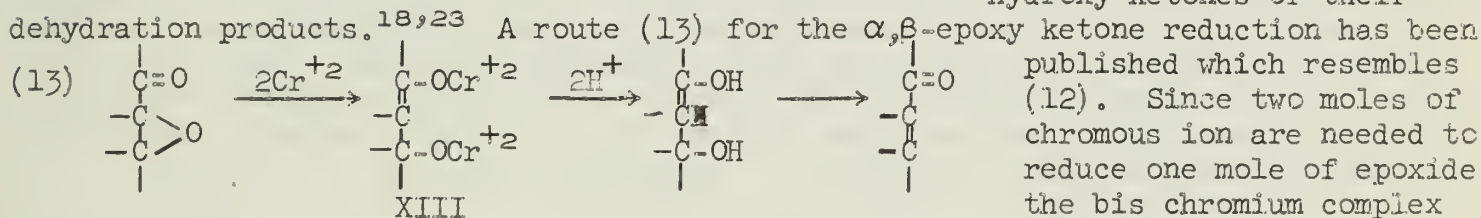


to 1,4-diphenyl-1,4-butanedione (20%), acetophenone (49%), dypnone (PhCOCH=C(CH₃)Ph) (29%), and 1,3,5-triphenylbenzene (trace). The authors favor (11) as the pathway for the formation of acetophenone while they propose a mechanism proceeding through an ionic species analogous to the benzylchromium ion for the formation of the coupling product. The latter route will be discussed later in detail. The other products mentioned probably result from the condensation of acetophenone. It is possible to formulate the reaction in an alternative stoichiometric manner (12).³



Conceivably XI is converted to XII by a mechanism already discussed (7 or 8).

α,β -epoxy ketones are reduced by chromous salts to the corresponding β -hydroxy ketones or their

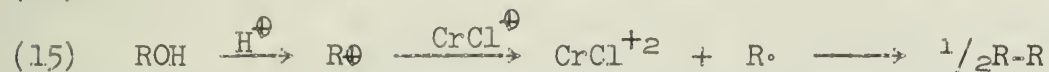
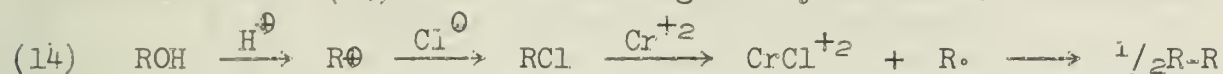


XIII was postulated. However, no other evidence was cited to support this proposed intermediate. If one accepts (13) then the reduction of α -halo ketones to alkanes by (12) should be given consideration in spite of the production of the benzylchromium ion intermediate. While the existence of $-\text{COCH}_2\text{Cr}^{+2}$ has not been confirmed, the possibility that it exists as a transitory intermediate can not be excluded in α -halocarbonyl reductions by Cr (II).

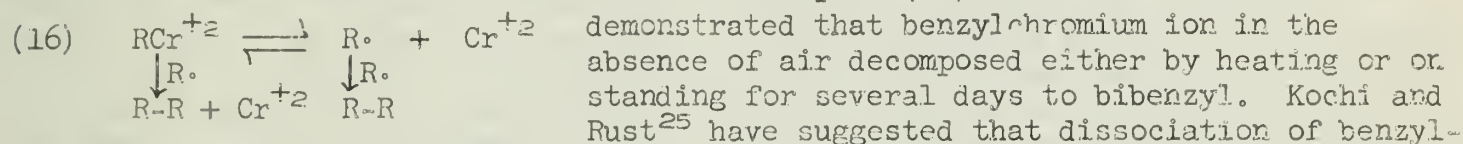
REACTIONS LEADING TO DIMERIC PRODUCTS

Work suggesting that dimers of corresponding organic halides are formed from free radical precursors has been reported by many investigators. Castro²⁴ showed that diphenylmethylcarbinol when mixed with chromous sulfate and perchloric acid gave diphenylethylene in 95% yield while under similar conditions when either diphenylethylene or diphenylmethylcarbinol was mixed with chromous sulfate, perchloric acid, and hydrochloric acid 2,2,3,3-tetraphenylbutane was obtained exclusively

and in yield. The reaction is assumed to proceed through reduction of an intermediate organic halide to a free radical species (14). It should be noted that the alternative route (15) could not be rigorously excluded. Castro and Kray¹⁰ later

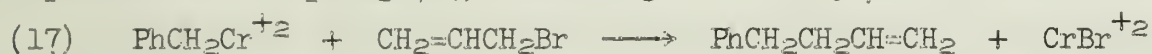


reported that optically inactive α -phenylethyl chloride or bromide gave identical mixtures of 85% meso and 15% dl 2,3-diphenylbutane. This result supports randomized free radical coupling as shown in (14). These authors also suggested that coupling may occur via a rapid reversible metal ion complex (16). Anet and LeBlanc⁹



demonstrated that benzylchromium ion in the absence of air decomposed either by heating or by standing for several days to bibenzyl. Kochi and Rust²⁵ have suggested that dissociation of benzylchromium ion may be responsible for the formation of adducts with acrylonitrile.

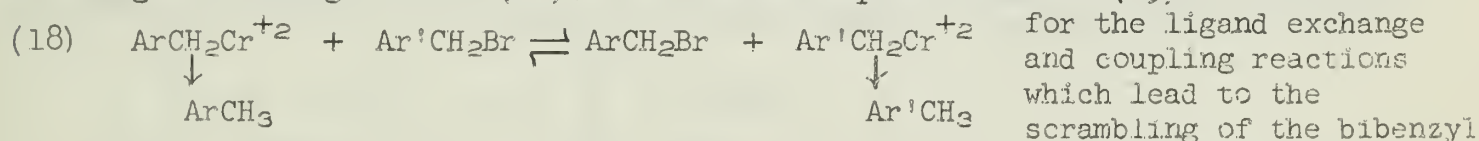
Slaugh and Raley⁶ showed that when benzylchromium ion reacts with allyl bromide at 0°C for two hours, 4-phenyl-1-butene is produced. They could not detect any bibenzyl or biallyl and therefore suggested that the following route is the most important for coupling (17). The higher bibenzyl/toluene ratios obtained in the



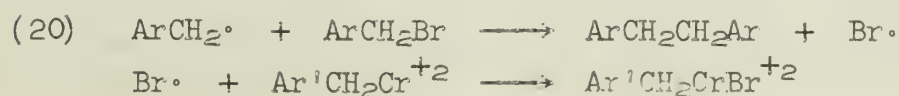
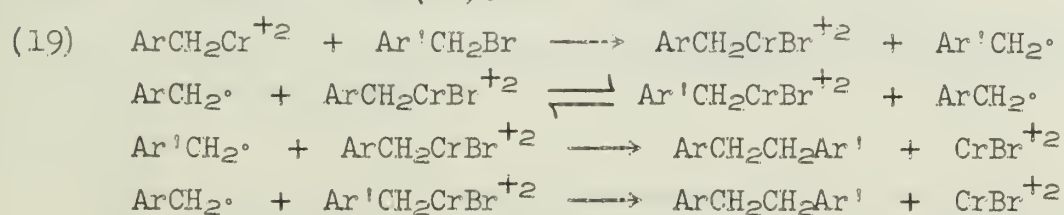
reduction of benzyl bromide and iodide relative to chloride seem to substantiate this proposal. One would expect that the halogen atom should play no effect in the amount of dimeric product if the product is derived from the thermal decomposition of benzylchromium ion.

Kochi and Buchanan⁷ agree with the general proposals of Slaugh and Raley. They found that a yellow brown solution of benzylchromium ion when mixed with benzyl bromide

in 80-90% ethanol-water at room temperature is converted to the green chromic solution at a rate estimated visually to be several times faster than the decomposition of benzylchromium ion. In this case the products of the reaction were toluene (30-40%) and bibenzyl (60-70%). When either *p*-xylyl bromide or benzyl bromide was reduced in 95% ethanol the corresponding alkanes were produced in better than 90% yield. An equimolar mixture of benzyl bromide and *p*-xylyl bromide under similar conditions gave better than 80% yield of the corresponding alkanes in addition to a small amount of various bibenzyls (5%). The bibenzyl fraction was substantially increased if *p*-xylyl bromide was added to a solution of benzylchromium ion under conditions similar to those described above. In addition to toluene and bibenzyl, large amounts of *p*-xylene, *p*-methylbibenzyl, and *p,p'*-dimethylbibenzyl were also formed. Similar, though not identical, results were obtained if benzyl bromide and *p*-xylylchromium ion were mixed. To explain the result, it was assumed that ligand exchange occurs (18). A reaction sequence such as (19) would account

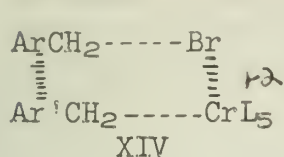


for the ligand exchange and coupling reactions which lead to the scrambling of the bibenzyl fractions. One might also anticipate that some coupling occurs by homolytic dissociation as outlined in (20).



Recently Neumer and Kahn²⁶ found that optically active α -phenylethyl chloride gives a threo-2,3-diphenylbutane fraction which was optically active. This observation is consistent with a

coupling process involving a four center transition state such as XIV. A related transition state would also accommodate the exchange reaction. It should be noted

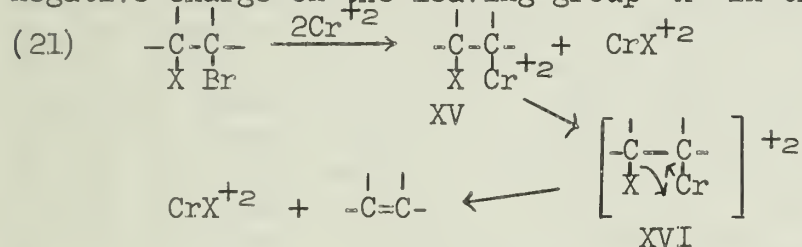


that this result appears inconsistent with Castro's work with α -phenyl halides mentioned previously.

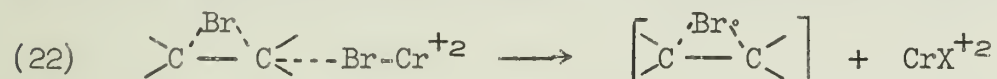
It is now of interest to consider whether the major route to formation of dimeric products is indeed through free radical coupling. Neumer and Aktipis¹⁰ have reported that "the same products were obtained" upon addition of a large quantity of a radical scavenger, namely trans-stilbene, to the Cr(II) reduction of benzal chloride. If their work is taken to mean the product ratio is invariant one could conclude that dimers form directly from undissociated ion-radical complexes. However, the authors did not report the yields in the reaction with scavenger to compare with the reaction carried out in the absence of scavenger. Slauch and Raley⁶ showed that if diphenylmethyl chloride is reduced with chromous chloride in aqueous dioxane with an added H-transfer agent such as ethylthioglycolate, the yield of diphenylmethane did not increase. It would seem that if a free radical mechanism were operative the radicals should be vulnerable to attack by such a good hydrogen donor. Quantitative work with scavengers is required before one can draw conclusions as to a mechanism by which products are produced.

REDUCTION OF VIC-DIHALIDES BY CR(II)

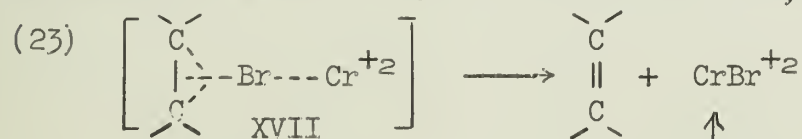
The pathway for Cr(II) reduction of vic-dihalides and halohydrins can be considered to be analogous to that of monohalides. The formation of a transient alkylchromium species such as XV would facilitate removal of an adjacent hydroxy or halide group by intramolecular 1,4 ligand transfer without development of a formal negative charge on the leaving group "X" in the transition state XVI.⁸ The most



striking feature of the reduction of vic-dihalides is the increased rate of the reaction when compared to similarly substituted monohalides. Castro and Kray²⁷ have attributed this rate enhancement to neighboring group participation (22). Removal



of the second halogen can be depicted in many ways (XVI, XVII, XVIII). The clean trans debromination of meso-2,3-dibromosuccinic acid to fumaric acid is interpreted as support for XVII. Castro's data on dibromobutanes support a trans elimination of Cr^{+3} and X^- from XVI. It should be noted, however, that Kochi and Mocadlo⁸



could not detect any free acetate development during the reductive elimination of 2-bromo-3-acetoxybutane.

CONCLUSION

There are several plausible mechanisms for chromous ion reductions. It is definitely known that the reduction of benzyl halides occurs through a benzyl-chromium ion; however, there is no conclusive evidence that a similar intermediate is formed during the reduction of other organic halides. The transfer of hydrogen from the chromium solvation sphere to form alkanes also seems well supported.

Whether dimeric products occur through a free radical or concerted process is still in doubt. More work must be completed on this problem. Neighboring group participation seems probable with many vic-dihalides with subsequent conversion of the resulting intermediate to products through several different pathways.

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Reported by Charles M. Leir

August 9, 1965

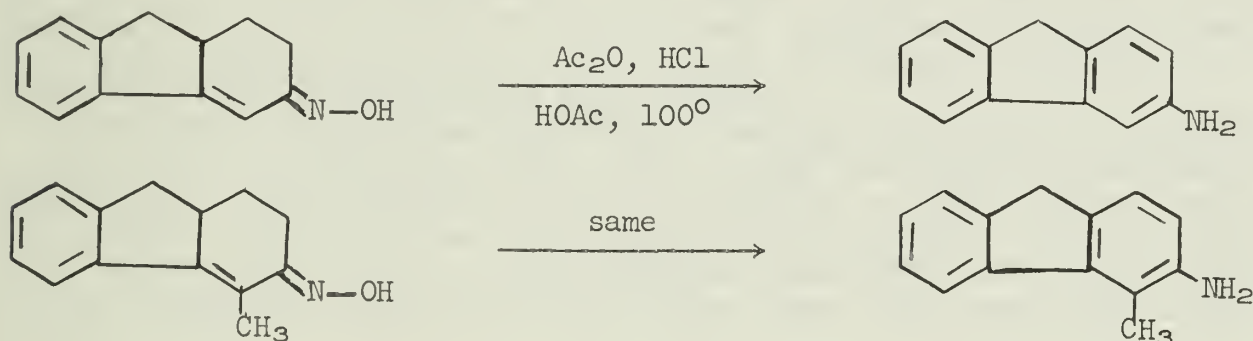
INTRODUCTION

The Semmler-Wolff aromatization is an unusual reaction in which cyclic ketoximes are converted to aromatic amines. In the case of six-membered ring oximes unsaturation (usually in a position α to the oximino group) is required in order for aromatization to occur. Cyclohexenone oximes and 1,2,3,4-tetrahydronaphthalenone oximes of this type have been the most widely studied substrates for this reaction. In these cases, derivatives of aniline and naphthylamine, respectively, are produced. However, a wide variety of other substrates also have been employed successfully to afford amine derivatives of anthracenes,¹ fluorenes,² quinolizinium salts,³ and thiophenes.⁴ Yields for the reactions are low in general (30-50%) when reported.

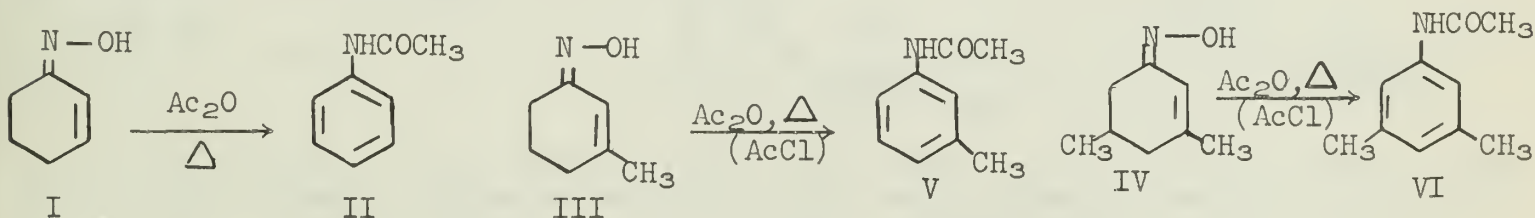
Although this reaction has been known and utilized for well over seventy years, no comprehensive review has been made,⁵ and surprisingly little work has been devoted to the elucidation of the mechanism of the transformation. It will be the purpose of this seminar to review the many examples of this reaction that have appeared in the literature, and to survey the mechanisms which have been suggested to be operative.

CYCLOHEXENONE OXIMES

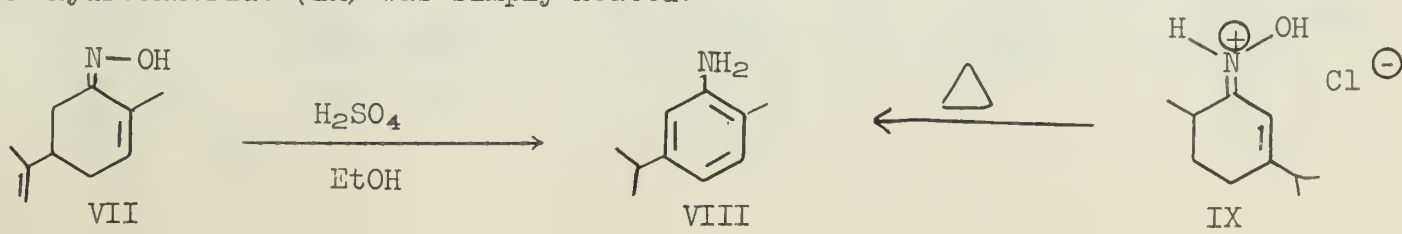
The conditions described in the literature for effecting the Semmler-Wolff aromatization are extremely diverse, although the most commonly employed reagent has been "Beckmann's mixture", which consists of a solution of acetic anhydride in acetic acid saturated with hydrogen chloride. Very recently, Davey and Keene were able to synthesize difficultly accessible 3-amino fluorenes in high yields using this technique.²



Many simpler derivatives of cyclohexenone oxime have been aromatized under a variety of other conditions. Most of this work, however, is very old. For instance in 1909, Kotz and Grethe found that cyclohexenone oxime (I) itself yielded acetanilide (II) upon heating under reflux in acetic anhydride. No additional catalyst was required. 3-Methyl and 3,5-dimethyl cyclohexenone oximes (III and IV, respectively) under the same conditions, or utilizing boiling acetyl chloride, afforded the corresponding substituted acetanilides (V and VI).⁷



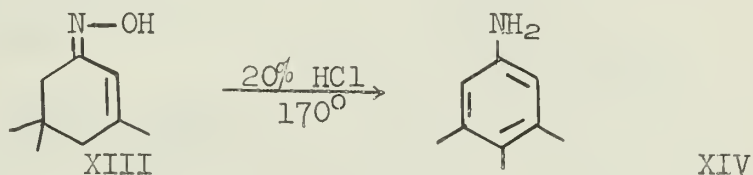
Wallach has employed H_2SO_4 - EtOH mixtures to effect the conversion of carvone oxime (VII) to carvacrylamine (VIII).⁸ This same product was obtained when dry carvenone oxime hydrochloride (IX) was simply heated.⁹



Wallach has reported that aqueous acid is capable of inducing the Semmler-Wolff aromatization.¹⁰ When isocarvone oxime (X) was subjected to 4% H₂SO₄ under reflux, an alcohol derivative of carvacrylamine (XI) was isolated. Carvone oxime (VII) under the same conditions supposedly yields the p-amino phenol XII as a product.¹⁰

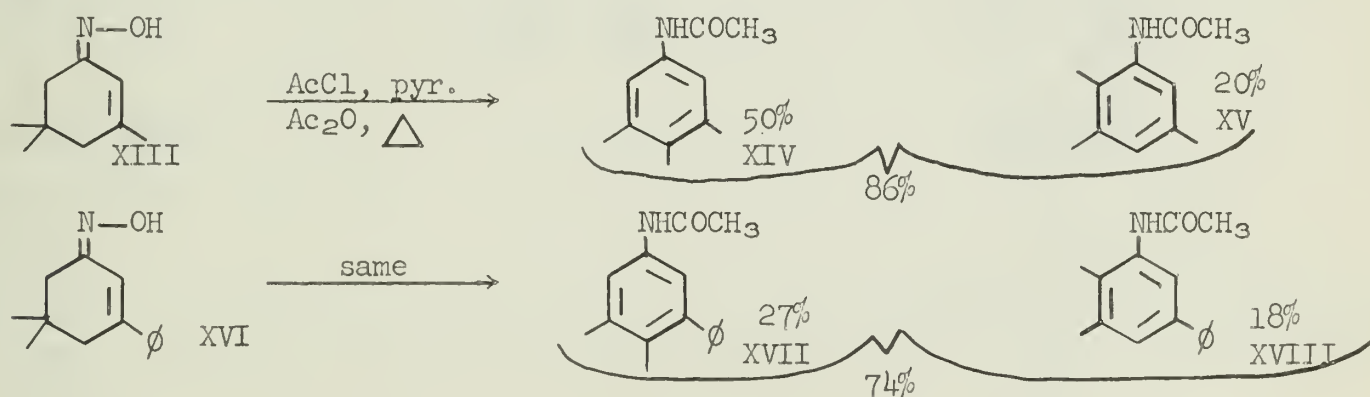


One of the most interesting examples of this reaction is the reported aromatization of isophorone oxime (XIII).⁷ In this compound, aromatization would appear to be blocked due to the presence of a geminal-dimethyl substitution. Nevertheless, Wolff claimed that heating this oxime in 20% HCl in a sealed tube at 170° afforded 3,4,5-trimethylaniline (XIV).⁷

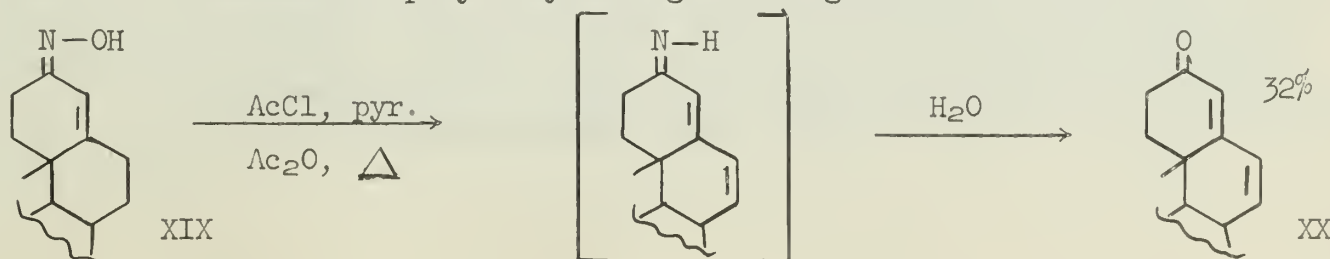


However, when this experiment was repeated recently, only isophorone was isolated and no amine could be detected.¹¹ This emphasises the need to exercise caution in accepting much of the early work in this area. In most cases, no yields of the products were reported, nor any mention made regarding the purity of solvents, reagents, etc. It is noteworthy that in some cases it is possible that structural assignments of both precursors and products are erroneous.

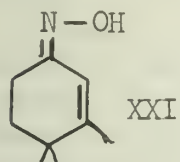
By altering the reaction conditions, Beringer and Ugelow¹¹ accomplished the aromatization of isophorone oxime (XIII). Upon warming equivalent amounts of oxime, pyridine and acetyl chloride in acetic anhydride, an 86% yield of crude acetanilide was obtained, from which two pure products were isolated: 3,4,5-trimethyl acetanilide (XIV) in 50% yield, and the 2,3,5-trimethyl isomer XV in 20% yield. Another experiment with 3,3-dimethyl-5-phenyl-2-cyclohexenone oxime (XVI) gave similar results (XVII and XVIII).¹¹



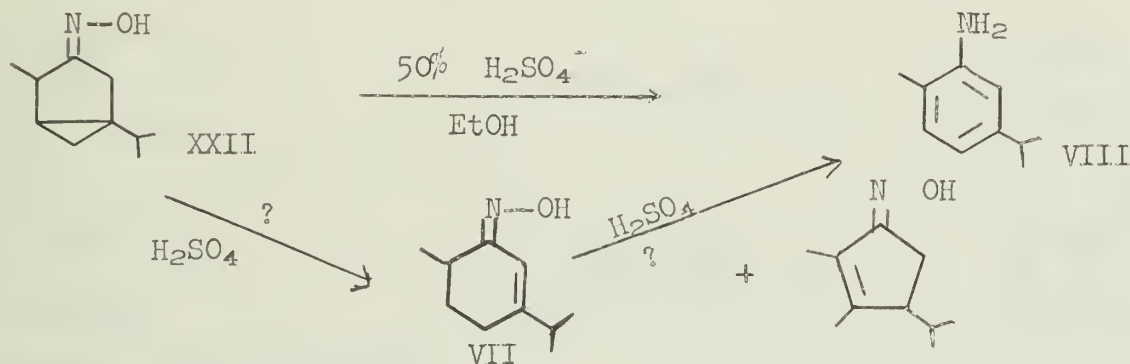
The location of the gem-dimethyl group would appear to be critical in view of some recent work by Bhatt. Cholestenone oxime (XIX), which contains a methyl group potentially capable of migration prior to aromatization, instead formed dienone XX in 32% yield under the conditions employed by Beringer and Ugelow.¹²



However, this behavior could be due to the presence of the adjacent six-membered ring in which dehydrogenation occurs faster than methyl migration. Perhaps a more suitable system in which to study this isomeric requirement would be 3,4,4-trimethyl-2-cyclohexenone (XXI) in which no such dehydrogenation is possible.



Another very interesting rearrangement was observed by Semmler upon treatment of thujone oxime (XXII) with 50% H_2SO_4 -ethanol. The product was carvacrylamine (VIII).¹³ However, it was not established whether the oxime rearranged directly into the aniline, or if there was possibly a prior rearrangement; since it has been recently shown that under acid conditions, thujone rearranges to carvenone and "isothujone."¹⁴ It is possible, then, that thujone oxime (XXII) first rearranged in acid to carvenone oxime (VII), and it is the latter compound which is the precursor for VIII.

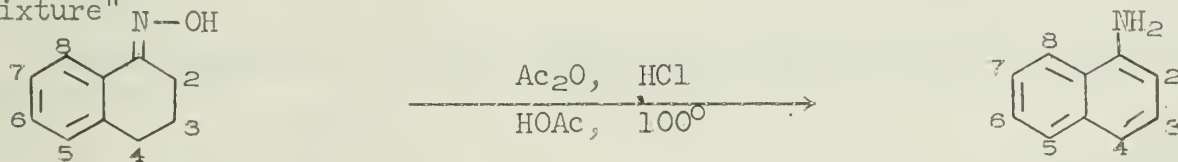


TETRALONE OXIMES

Many 1,2,3,4-tetrahydronaphthalenone oximes (tetralone oximes) with various substituents on the aromatic nucleus have been successfully aromatized with "Beckmann's mixture" (Ac_2O , AcOH , HCl , 100°) to the appropriately substituted naphthylamines. The results are summarized in Table I.

TABLE I

Substituted tetralone oximes converted to substituted naphthylamines by "Beckmann's mixture"



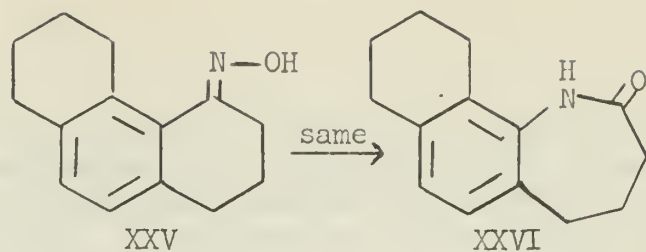
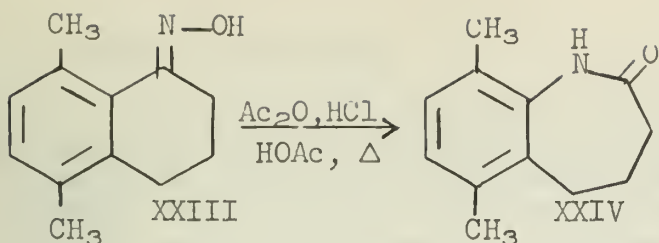
TETRALONE OXIME

unsubstituted
5-nitro
7-nitro
6-chloro
7-chloro
6-methoxy
7-methoxy
5-methoxy-7-methyl
6,7-tetramethylene
5-nitro-6,7-tetramethylene

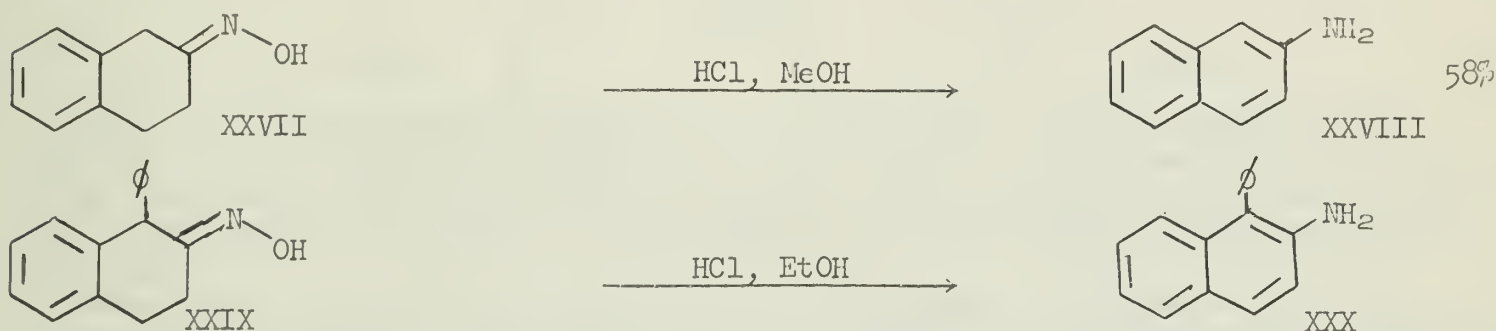
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Schroeter and coworkers¹ have demonstrated a possible steric requirement for this reaction in their attempted aromatization of some 8-substituted tetralone oximes. 5,8-Dimethyl tetralone oxime (XXIII) under the influence of "Beckmann's mixture" underwent a Beckmann rearrangement to yield the lactam XXIV instead of the expected naphthylamine. The octahydrophenanthrenone oxime XXV gave similar results and was converted to XXVI.¹

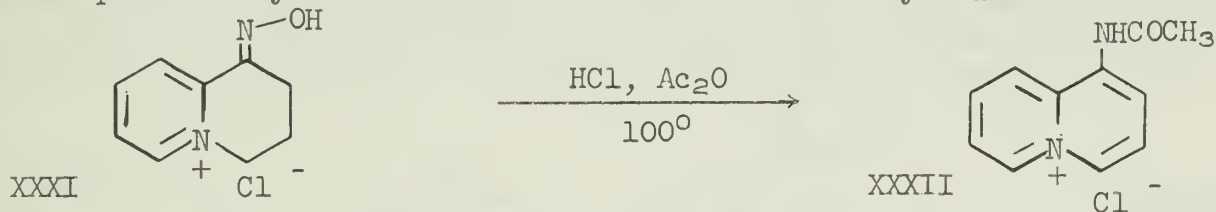


Zaugg, et al.¹⁸ attempted the aromatization of 2-tetralone oxime (XXVII), a compound in which the aromatic system is no longer in conjugation with the oximino group. When warmed with dry HCl in absolute ethanol, no β -naphthylamine (XXVIII) was detected. Recently, however, Rosen and Green²⁶ successfully aromatized XXVII in 58% yield using methanol-HCl under reflux for one hour. 1-Phenyl-2-tetralone oxime (XXIX) under essentially the same conditions was also converted smoothly to the corresponding naphthylamine XXX.¹⁸

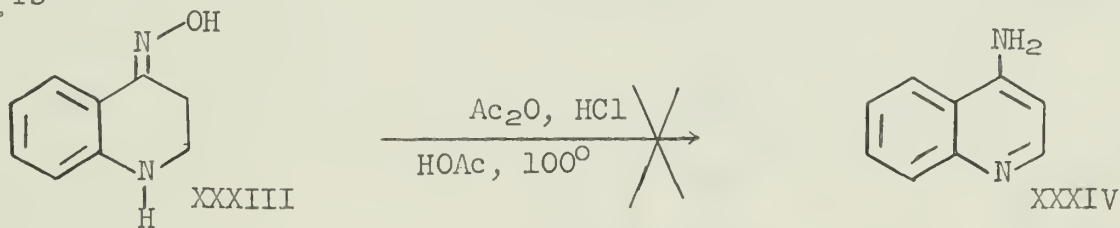


MISCELLANEOUS CYCLIC KETOXIMES

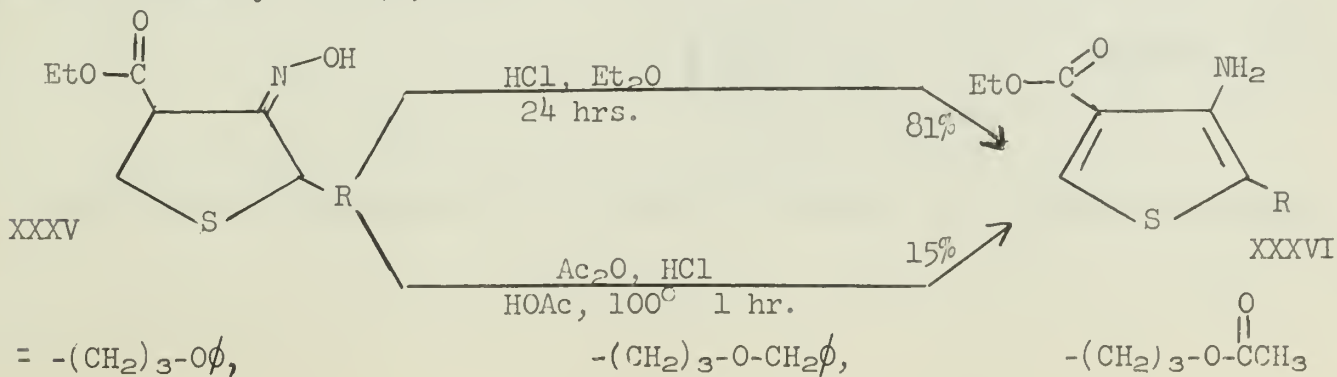
Collicutt and Jones have recently reported that the 1-amino quinolizinium salt XXXII was produced by the action of HCl on an acetic anhydride solution of oxime XXXI.³



Under essentially the same conditions, however, XXXIII yielded no aromatized derivative.¹⁹



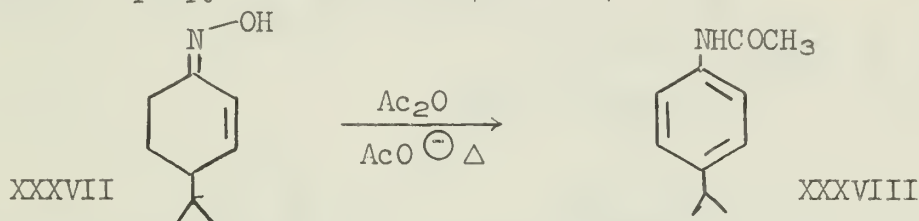
A variety of conditions were employed by Cheney and Piening to effect the aromatization of the heterocyclic ketoxime XXXV. It was found that yields of 79-81% of amino thiophenes XXXVI were obtained with anhydrous HCl in ether, while "Beckmann's mixture" gave much lower yields (15%).⁴



PROPOSED MECHANISMS

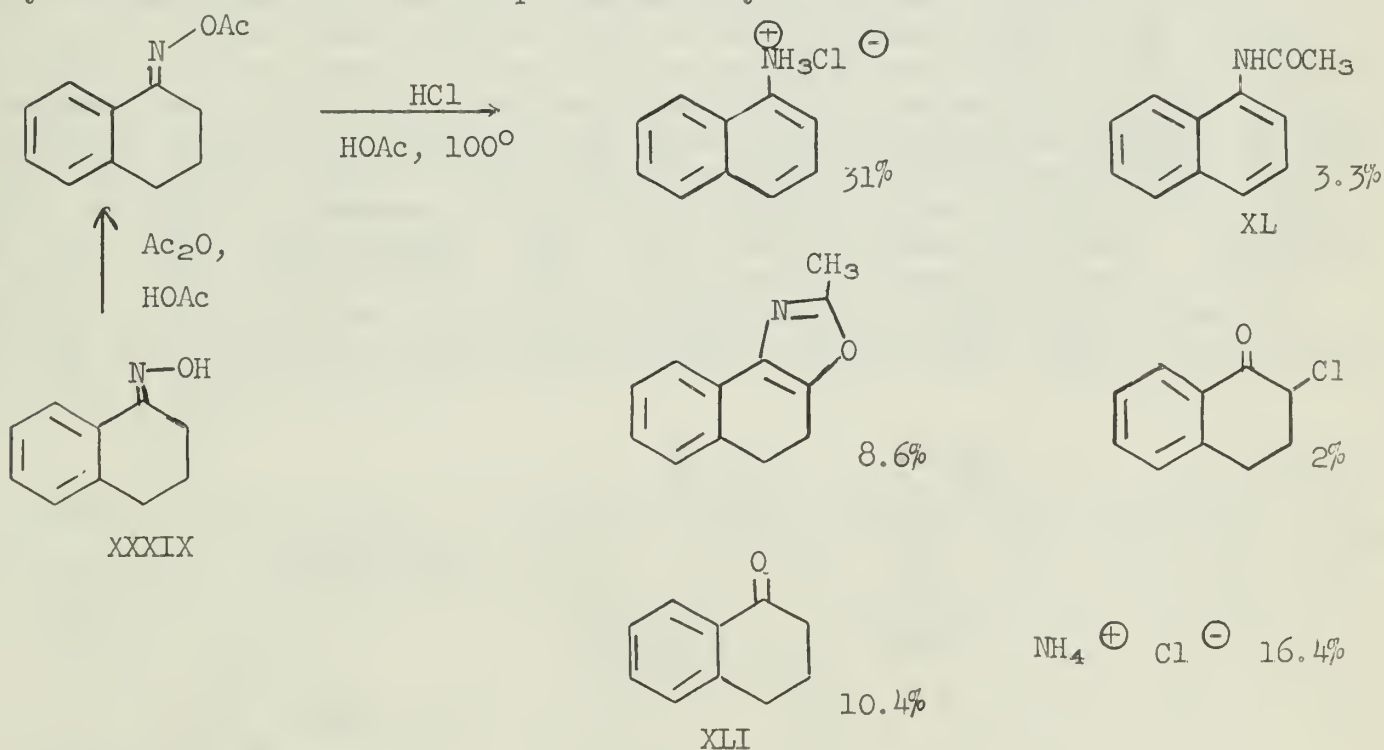
In general, the conditions that have been employed to effect the Semmler-Wolff aromatization may be divided into three categories: 1) a solution of the oxime in ether or alcohol with an excess of acid, 2) equivalent amounts of oxime and acetic anhydride in acetic acid with an excess of HCl, 3) a solution of the oxime in 100% acetic anhydride or acetyl chloride, or a mixture of both. It is conceivable that a distinct and different mechanism may apply for each of these three reaction conditions.

A possible fourth category was investigated by Cooke and Macbeth who used acetic anhydride and sodium acetate to effect the aromatization of 4-isopropyl-2-cyclohexenone oxime (XXXVII) into 4-isopropyl acetanilide (XXXVIII).²⁰

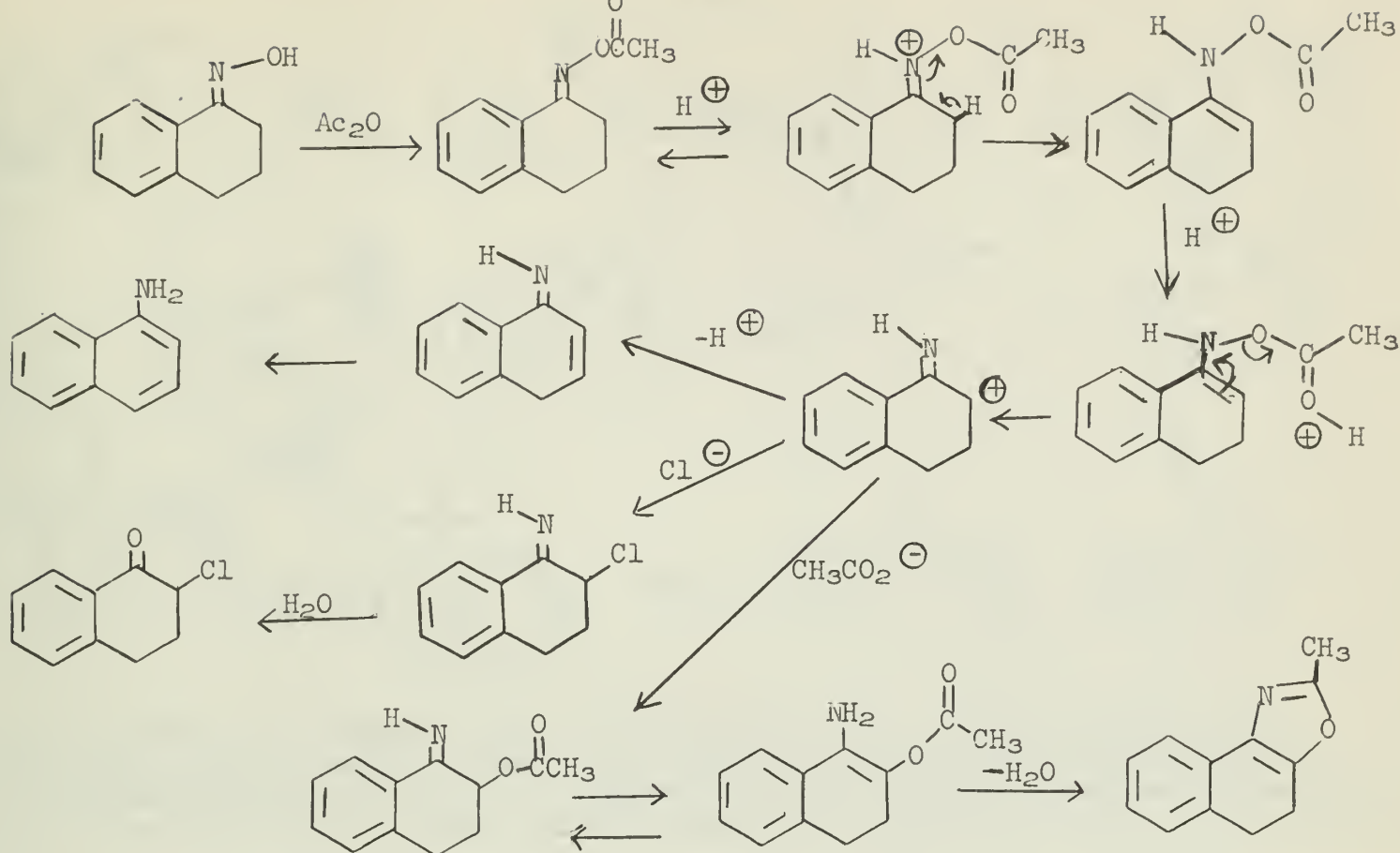


This is the only reported example of a possible base catalysed Semmler-Wolff reaction, but the reaction was never run in the absence of added acetate ion to see if it were really a catalyst. It is conceivable that it may perform no function at all, since 100% acetic anhydride had already been shown to effect aromatizations of this type.^{7,11}

When acetic anhydride or acetyl chloride is employed, the first step in the aromatization sequence is the formation of an intermediate O-acetyl oxime. Vorozhtzov and Koptiung in some very careful experiments with α -tetralone oxime (XXXIX) isolated this O-acetyl derivative (XL) from its acetic acid solution. Upon heating this acetate under reflux in absolute acetic acid, no reaction occurred; and it was almost completely recovered unchanged. However, when HCl gas was added, aromatization occurred. From a large scale reaction, several other by-products in addition to the naphthylamine were isolated. The products and yields are listed below.²¹

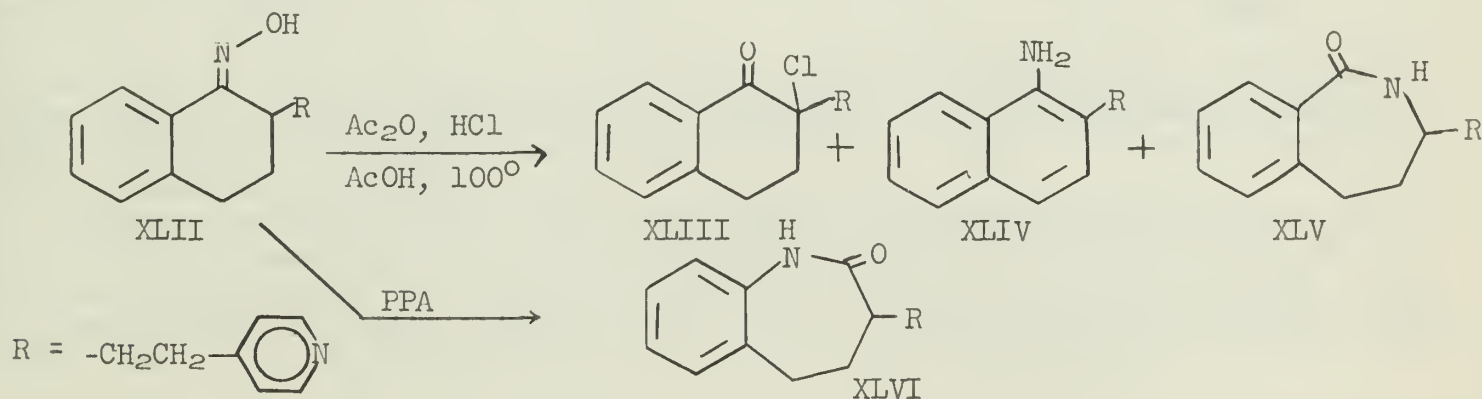


The authors rationalized these products according to the following scheme:

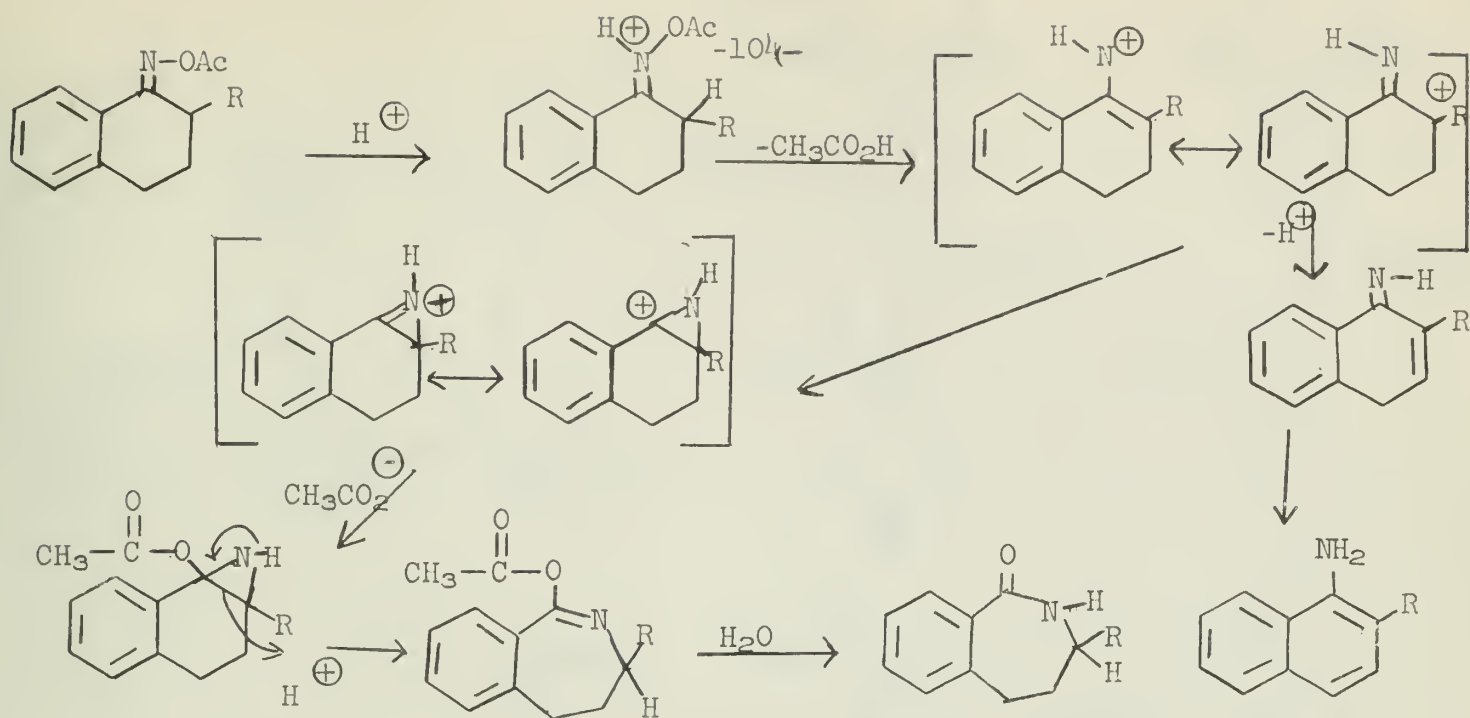


Formation of α -tetralone (XLI) cannot be explained by this mechanism, and indeed the formation of the other by-products cannot be regarded as proof that they all arose from some common intermediate as was proposed.

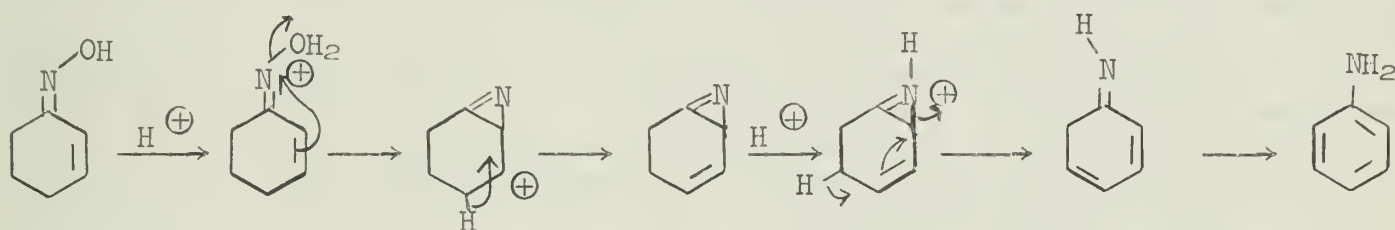
It is interesting to note that no Beckmann rearrangement product was detected by these workers. Often this reaction occurs to at least some extent under the acid conditions usually employed. In some instances the lactam resulting from a Beckmann rearrangement actually becomes the predominant product, especially when the nature of the acylating agent is changed. This behavior was demonstrated recently by Bauer and Hewitson. These workers treated the substituted tetralone oxime XLII $R = [\beta-(4\text{-pyridyl}) \text{ ethyl}]$ with "Beckmann's mixture" and obtained three products: the chloro-ketone XLIII (8%), naphthylamine XLIV (27%) and the lactam XLV (56%). Absolutely none of the isomeric lactam XLVI could be detected as a product in this reaction. In contrast, lactam XLVI was the major product obtained (56-72% yield) when the oxime XLII was treated with polyphosphoric acid. In this case, none of its isomeric lactam XLV could be detected.²²



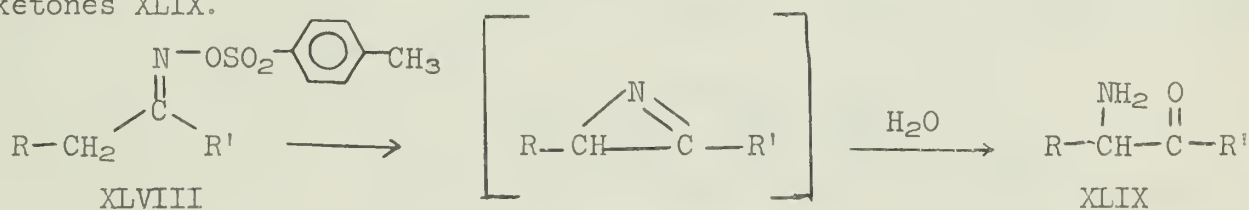
The authors merely modified the Vorozhtsov-Koptiung mechanism²¹ slightly to explain the formation of lactam XLV but felt the other products were formed in a manner similar to that proposed earlier.



R. T. Conley has suggested that three-membered ring (azirine) intermediates of the type proposed earlier by Bauer and Hewitson are involved in the formation of the aromatized products as well. He suggests that the following mechanism is operative in the conversion of non-acylated oxime to aniline in acid:²³

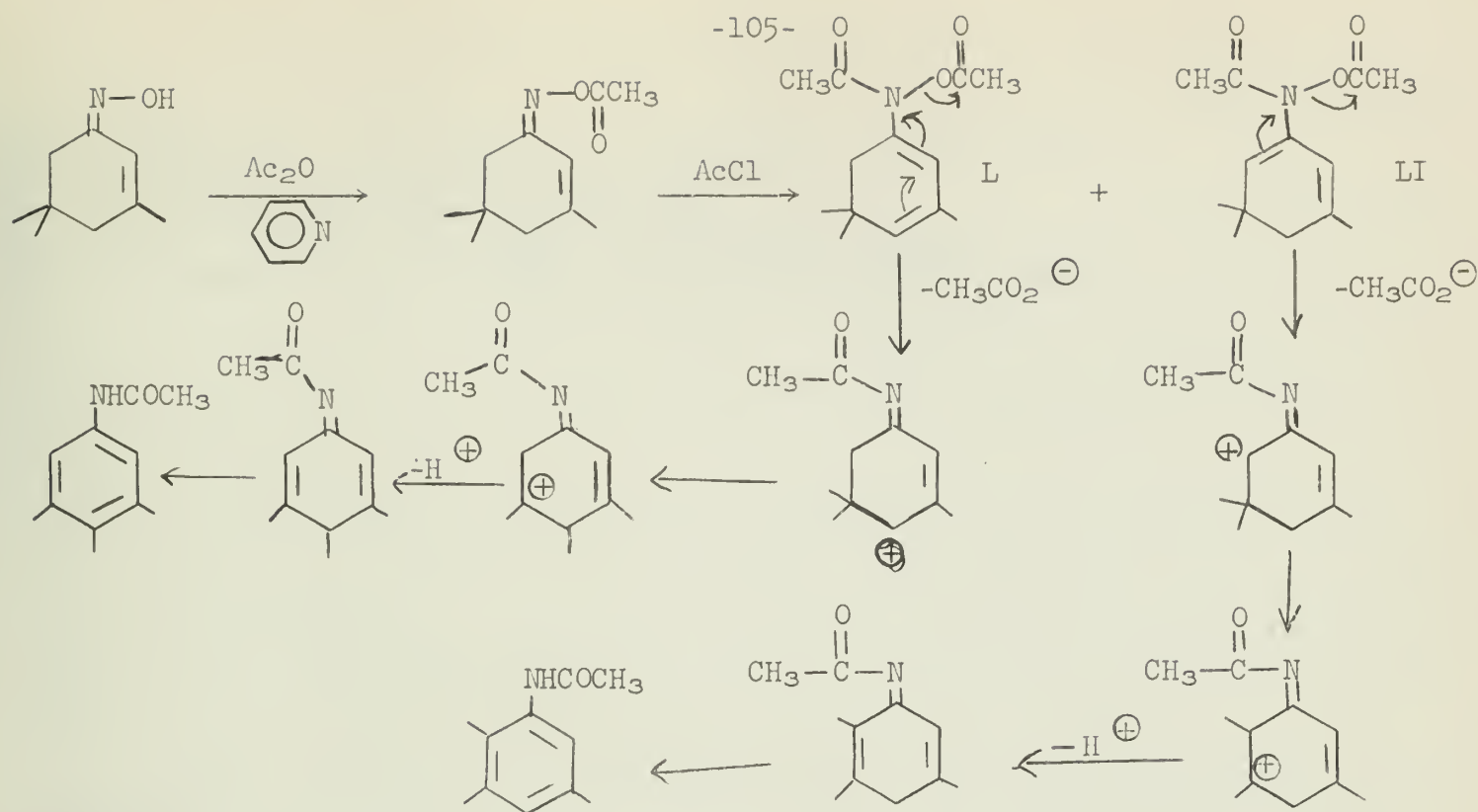


In support of this scheme, Conley cited the fact that azirines have been isolated as intermediates in the Neber rearrangement.²⁴ In this reaction, ketoxime tosylates containing an active α -methylene group such as XLVIII are converted to the corresponding α -amino ketones XLIX.



However, a Neber reaction is conducted in strong base, while the Semmler-Wolff rearrangement is usually carried out in strong acid. It is questionable whether a direct analogy can be drawn between the two reactions since the conditions employed are so drastically different.

Beringer and Ugelow believe that an entirely different mechanism must be operative,¹¹ when aromatization is effected under essentially neutral conditions as in the cases where oximes are heated in 100% Ac_2O or AcCl , or a mixture of both. The key intermediates in their proposed scheme for the aromatization of isophorone oxime (VIII) were O- and N-diacetyl derivatives of the oxime (L and LI).¹¹



CONCLUSION

It is evident from the foregoing discussion that the various proposed "mechanisms" are all rather arbitrary with little experimental evidence to support or disprove any one of them. It is safe to say that the detailed mechanism of the Semmler-Wolff aromatization remains to be established. Perhaps what is needed most is a thorough investigation of the kinetics of the reaction including solvent effects and substituent effects (particularly in the case of tetralone oximes). Stereochemical requirements, if any, about the C-N double bond are entirely unknown. The effect of changes in polarity of the oxime acylating agent has received limited attention, but scarcely any information was obtained.^{1,15,25} Until a serious mechanistic study of this reaction is undertaken, it will remain as it has for the last seventy-three years -- a novel, though often unsatisfactory synthetic tool.

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THE NON-CLASSICAL FREE RADICAL

Reported by Z. M. Holubec

August 11, 1965

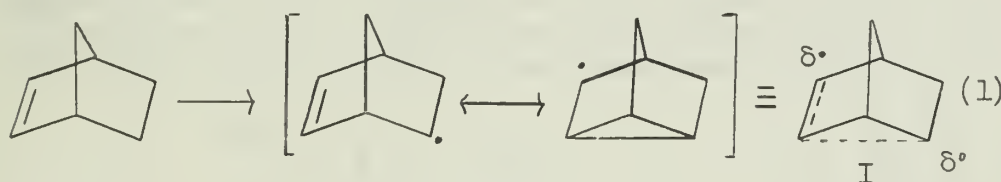
INTRODUCTION

As workers in the field of carbonium ion chemistry were demonstrating the wide applicability of the concept of the non-classical carbonium ion in explaining product distribution, stereochemistry, and rate enhancement toward solvolysis of certain molecules, investigators in the field of free radical chemistry began examining the analogous free radical systems for similar phenomena. Although the literature concerning the latter field is not as voluminous as that for carbonium ions, a great deal of useful information regarding the properties of free radicals has been obtained.

Several excellent reviews dealing with free radical rearrangement,¹⁻³ formation of carbon-carbon bonds⁴ and carbon-hetero bonds⁵ through radical processes were recently published. A comprehensive monograph⁶ covering the literature on solution free radical chemistry up to approximately 1956 is also available. This discussion will be limited primarily to the question of non-classical free radicals in bicyclic systems and its relationship to the observed rearrangements and the bridged halogen radical in halogenation and hydrohalogenation reactions.

THE NON-CLASSICAL FREE RADICAL IN BICYCLIC SYSTEMS

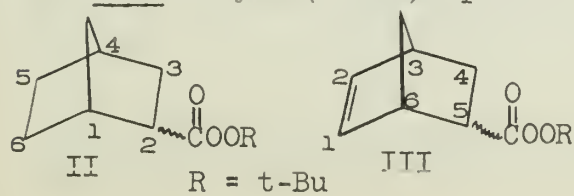
Carbonium ions in the rigid skeletal structures of bicyclic systems have attracted a great deal of attention. An excellent review concerning this subject has recently appeared.⁷ Of the large amount of evidence supporting the existence of the non-classical carbonium ion in these systems the most convincing is the tremendous rate enhancement observed in the solvolysis of exo-substituents and the demonstration that the rearranged products obtained can be rationalized on the basis of a single intermediate species, the mesomeric cation. Presumably, the former effect is due to sigma- or homoallylic pi-bond participation in the transition state. It is not unexpected that the same approach should be used by the workers in the free radical field in seeking evidence for or against the existence of a similar rate or product determining intermediate in bicyclic free radicals. Roberts and coworkers⁸ appear to be the first to have suggested the possibility of a non-classical radical in their work on the benzoyl peroxide initiated reaction of norbornene with N-bromosuccinimide in carbon tetrachloride. They found that 3-bromonortricyclene was produced in 27-40% yield. It was suggested that the orientation of orbitals in the rigid bridged-ring system favored interaction with the radical site:



Several other workers,⁹⁻¹⁴ studying free radical reactions of bicyclic derivatives in the early 1950's, failed to find re-

arranged products similar to those found in the analogous carbonium ions. Berson and coworkers,¹⁵ however, point out that in most of the reactions described earlier the yields of identifiable products are only moderate and that it is difficult to decide whether or not rearrangement is a prohibitive process.

Anchimeric assistance in the decomposition of 2-norbornyl- and 5-norbornenyl peroxyates and peroxides was investigated by Martin and DeJongh¹⁶ and by Hart and Chloupek,¹⁷ respectively. Martin and DeJongh compared the rates of homolytic cleavage of bonds exo and endo to the ethano bridge in the t-butyl peresters of exo- and endo-bicyclo(2.2.1)heptane-2-carboxylic acid (IIx and IIIn) and exo- and endo-



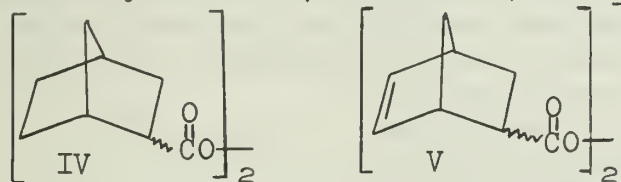
bicyclo(2.2.1)hept-5-ene-2-carboxylic acid (IIIx and IIIIn). As in the carbonium ion analogue,⁷ participation by the C1-C6 single bond or C1-C2 double bond should be reflected in the rate of decomposition and the activation parameters of the

exo and endo pairs. If there is no sigma- or pi-bond participation then the rates and activation parameters should be the same in the decomposition of each pair. These predictions are based upon the investigations of Bartlett and his students.¹⁸⁻²¹ In the transition state of a concerted decomposition there is of necessity a restricted rotation around bond b because elimination of the alkyl and t-butoxy radicals must be trans. There is no such restriction in a stepwise elimination. The mechanism by which this decomposition occurs is characterized by the values of the activation parameters ΔH^* and ΔS^* . In a mechanism involving no rotational restrictions in the transition state, the values of ΔH^* were found to be greater than 35 kcal/mole and ΔS^* of greater than 13 e.u. A concerted mechanism, on the other hand, is characterized by values of ΔH^* of 30-35 kcal/mole and ΔS^* of 6-13 e.u.

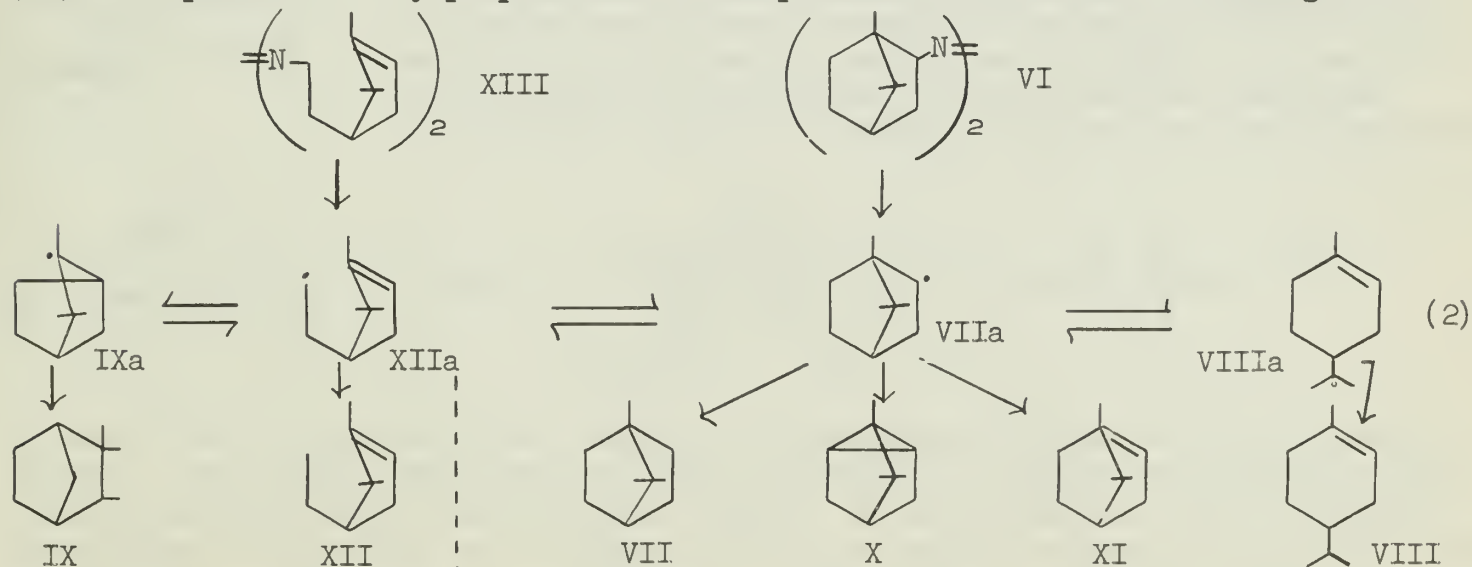
The kinetic experiments of Martin and DeJongh in cumene demonstrated that the rates of decomposition of each of the two pairs were essentially identical. The calculated ΔH^* for IIx and IIIn were 31.4 and 31.1 kcal/mole while the ΔS^* was 7 and 6 e.u., respectively. For IIIx and IIIIn the corresponding ΔH^* values were found to be 33.0 and 32.6 kcal/mole and the ΔS^* , 11 and 9 e.u., respectively. On the basis of these results, Martin and DeJongh concluded that decomposition proceeds through a concerted mechanism and that it is not energetically more favorable for an exo bond to undergo scission than it is for an endo bond. Therefore, neither sigma- nor pi-participation can be construed to be a significant driving force in these reactions.

Recently, Bartlett and McBride²² reinvestigated the decomposition of IIx and IIIn. Although conclusions regarding the sigma- and pi-participation were the same as those of Martin and DeJongh, they found that IIx decomposes at about three times the rate of IIIn. The activation parameters, however, still fall well within the range predicted by model compounds.

Similar conclusions were reached by Hart and Chloupek¹⁷ after investigating the kinetics of the decomposition of the diacyl peroxides from exo- and endo-norbornane-2-carboxylic acid (IVx and IVn) and exo- and endo-norbornene-5-carboxylic acids, (Vx and Vn). They found that although IVx decomposes at 7-10 times more rapidly than IVn, the peroxides Vx and Vn decompose at essentially identical rates. The observed acceleration of IVx over IVn was attributed to a steric factor.



Several workers^{15,23-30} studied the behavior of the 2-norbornyl and related radicals under a variety of conditions. Berson, Olsen, and Walia¹⁵ found that among the products isolated from the decomposition of 2-azocamphane, bornane (VII), 1-p-menthene (VIII), 2,3,3-trimethylnorbornane (IX), tricyclene (X), and bornene (XI) were present. They propose that these products arise in the following manner:



The radical XIIa was prepared independently by decomposition of XIII. Under the conditions used to decompose VI, azo compound XIII yielded a complex mixture of

products in which VII and IX were present. Hence, it was concluded that VIIa is probably the immediate product of the decomposition of VI, and an equilibrium between VIIa and XIIa must exist.

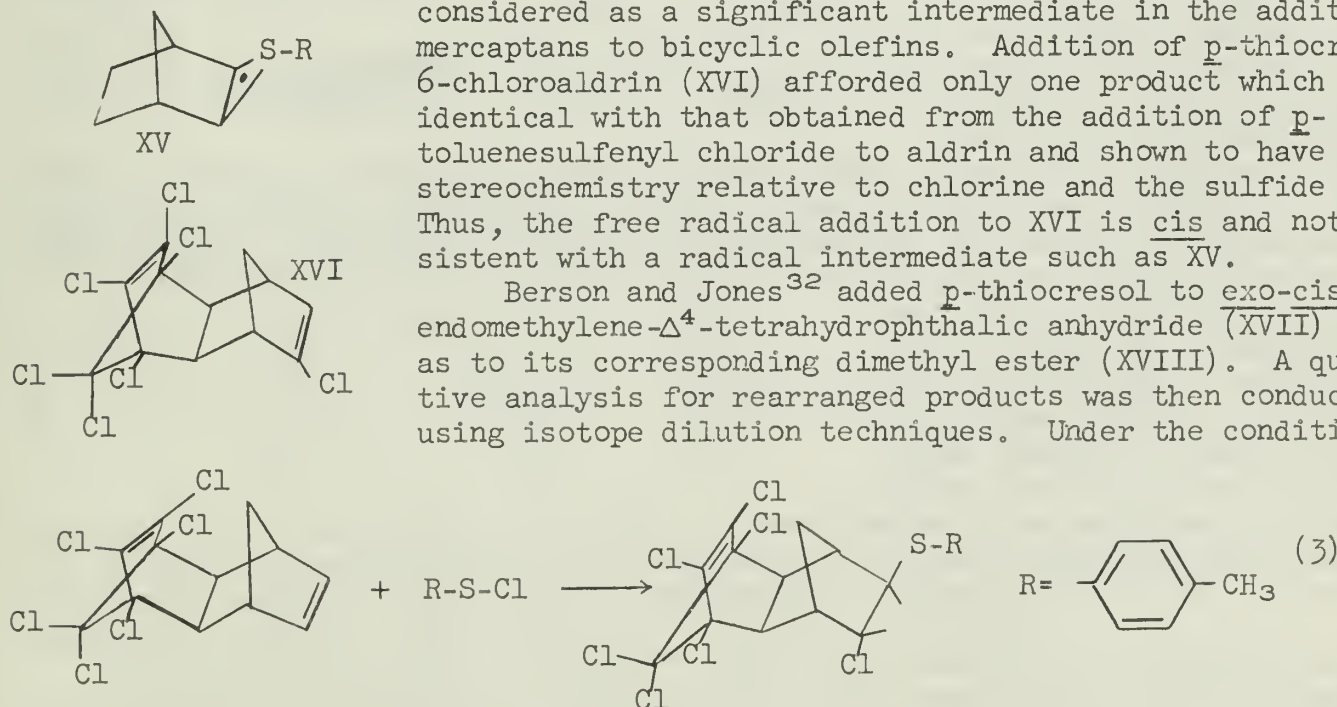
The question which immediately arises is what part, if any, a mesomeric free radical (XIV) plays in the observed rearrangement. Berson and coworkers concluded that no analogy can be drawn between this and the structurally similar carbonium ion process. The decomposition of VI and XIII occur at rates which are essentially the same as those of simple model compounds in which anchimeric assistance is absent. Furthermore, in the rearrangement of VI to IX, there is no stereospecificity or selectivity and both possible stereoisomers are produced. This observation makes it difficult to reconcile the observed products with XIV as the sole intermediate. In addition, ratios of the products obtained from the decomposition of VI and XIII clearly show that the amount of a given hydrocarbon is dependent on the azo compound decomposed. This suggests that a non-mesomeric radical is not rapidly converted to a common mesomeric product-forming intermediate. If a common intermediate formed from either azo compound, its fate would be independent of its precursor.

It may be significant that the ratio of any two products on a given side of the dotted line in the mechanistic scheme (2) is independent of the time and source of radicals while the ratio of any two products on opposite sides of the dotted line, while also independent of time, is not independent of the source of the radicals. For these ratios to be independent of starting material, a very rapid conversion of XIIa to VIIa or a common intermediate would be anticipated. Therefore, it was concluded that at least the major portion of the observed rearrangement must be going through classical radicals.

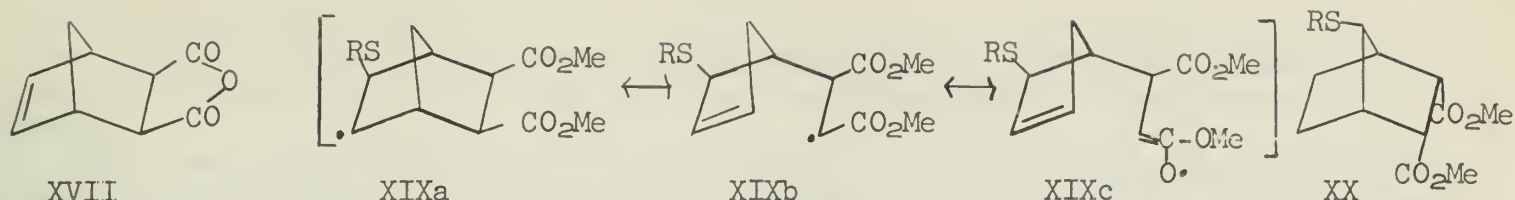
Research groups under the direction of Cristol and Berson sought to provide evidence for or against the non-classical free radical in the norbornyl system by radical additions to norbornenes. Cristol and Brindell²⁴ have shown that addition of *p*-thiocresol to norbornene yields only *exo*-norbornyl-*p*-tolylthioether in 85% yield. Thus, no rearrangement analogous to the Wagner-Meerwein occurred and an intermediate such as XIV need not be invoked in order to rationalize the data. Cristol and Arganbright²⁵ also demonstrated that a radical such as XV need not be

considered as a significant intermediate in the addition of mercaptans to bicyclic olefins. Addition of *p*-thiocresol to 6-chloroaldrin (XVI) afforded only one product which was identical with that obtained from the addition of *p*-toluenesulfonyl chloride to aldrin and shown to have *trans* stereochemistry relative to chlorine and the sulfide group.³¹ Thus, the free radical addition to XVI is *cis* and not consistent with a radical intermediate such as XV.

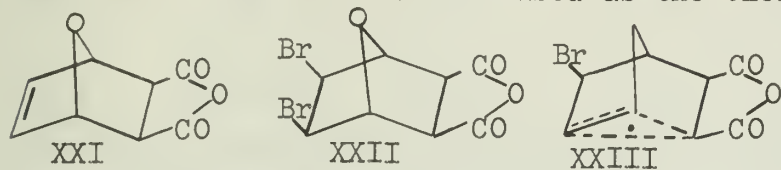
Berson and Jones³² added *p*-thiocresol to *exo*-*cis*-3,6-endomethylene- Δ^4 -tetrahydrophthalic anhydride (XVII) as well as to its corresponding dimethyl ester (XVIII). A quantitative analysis for rearranged products was then conducted using isotope dilution techniques. Under the conditions used



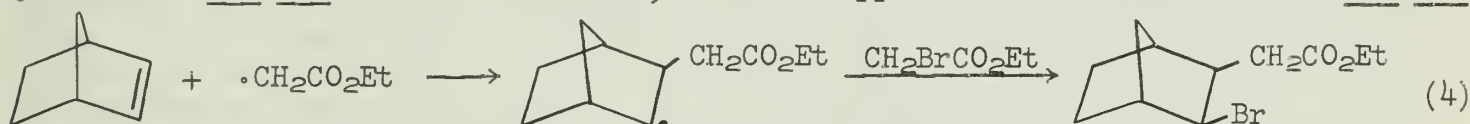
by these workers, the method was capable of detecting as little as 0.6% rearranged product. The authors postulate that XVII and XVIII are capable of sustaining a free electron because of the delocalization (XIXa-c) in the transition state leading to rearrangement. However, the experiment failed to produce any *endo* diester, XX, which would have been produced if rearrangement occurred. These workers concluded that delocalization shown by structures XIX does not play a significant role even under what is presumed to be the most favorable of conditions.



Berson and Swidler²⁸⁻²⁹ found that the bromination of exo-cis-3,6-endo-oxo- Δ^4 -tetrahydrophthalic anhydride (XXI) yields 36% of the cis dibromide XXII. Control experiments showed that XXII formed as a result of a free radical process. The same reaction occurs when XVII is used as the olefin.³⁰ Since repulsive non-bonded interactions of the eclipsed bromines of XXII should result in a higher activation energy in a mechanism involving random attack on a classical radical intermediate, the workers felt that a

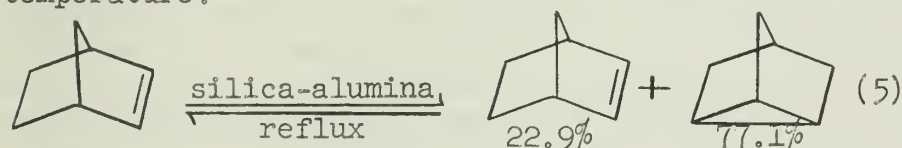


powerful stereoelectronic factor leading to XXII was operative. They proposed that the non-classical radical XXIII intervened as a product determining species. Walling,³³ however, notes that the stereochemistry is apparently the same as that observed by Weinstock³⁴ who found that addition of ethylbromoacetate to norbornene yields the exo-cis derivative. Thus, it would appear that formation of the exo-cis

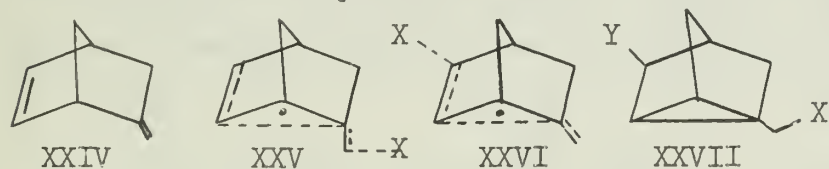


derivative is a manifestation of a steric rather than a stereoelectronic effect.

Because of the favorable position of the homoallylic double bond, the 5-norbornenyl free radical has attracted much attention from workers searching for evidence for non-classical free radicals.^{16-17,26-27,35-40} In almost all cases studied the 5-norbornenyl radical gives predominantly the nortricyclene rearranged product. This result is hardly surprising in view of the thermodynamically favored product when norbornene is equilibrated in presence of silica-alumina at reflux temperature.⁴¹



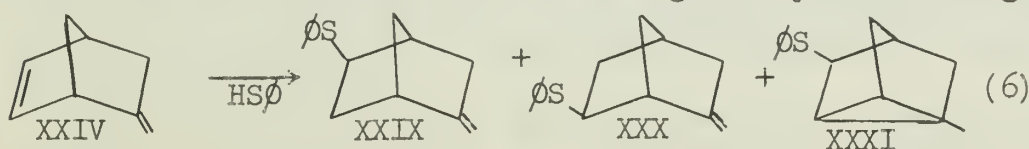
addition through delocalized species XXV and XXVI. Huyser and Echegaray²⁷ found that the exocyclic double bond is more reactive toward free radical addition of carbon tetrachloride, chloroform, and bromotrichloromethane and that the predominant product is the nortricyclene derivative XXVII. The conclusion regarding the relative



reactivity of the two olefinic bonds was confirmed by a competition experiment between 2-methylenenorbornane (XXVIII) and norbornene. It was found that the exocyclic double bond was about four times as

reactive as the endocyclic double bond. These workers also published evidence that the delocalized species XXV was not involved in the homoconjugative addition by a competitive reaction involving XXIV and XXVIII. It was observed that the total reactivity of XXIV is only 28% greater than that of XXVIII.

Recently, Cristol and coworkers²⁶ studied the addition of thiophenol to XXIV and found that the endocyclic double bond is more reactive toward this reagent. The nature of the intermediate was investigated by determining the effect of mercaptan concentration on the ratio of XXIX to XXXI. If the radical intermediate is non-classical, then there should be no effect on the ratio. If, on the other hand, two classical radicals are



concentration on the ratio of XXIX to XXXI. If the radical intermediate is non-classical, then there

involved, dilution of mercaptan will result in a slower chain transfer and favor isomerization to XXXI. Dilution of mercaptan produced a significant decrease in the ratio. Therefore, it was concluded that a non-classical radical was not involved.

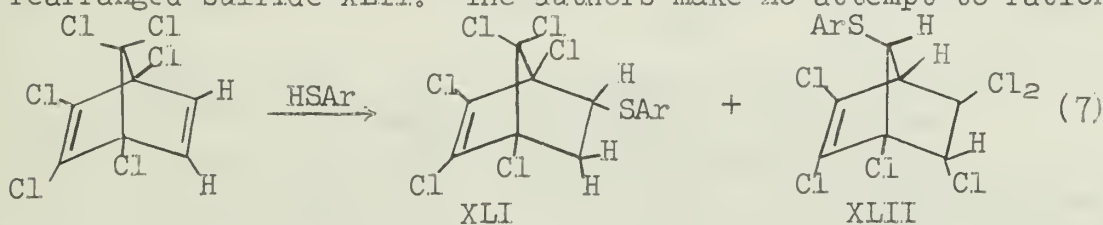
Wilt and Levin³⁵ generated radicals XXXII-XXXV via the decarbonylation of the corresponding aldehydes. They found that only XXXIII rearranged and then only to nortricyclene. In spite of low yields of hydrocarbons (typically less than 10%), they concluded that the non-classical radical XXVI or the kinetically equivalent



rapid equilibration of classical radicals XXXVII and XXXVIII were intermediates. This conclusion was drawn on the basis of the observation that dilution of substrate had no significant effect on the ratio of norbornene to nortricyclene. Earlier, Cristol and Brindell³⁶ had shown that in the addition of *p*-thiocresol to norbornadiene the ratio of the norbornene to the nortricyclene derivative decreased as the concentration of mercaptan was lowered. They concluded that neither the non-classical radical nor the equilibration can be involved in the product determining step. In subsequent work, Cristol and Davies³⁷ showed that this conclusion is valid. Addition of various halides to norbornadiene gives 1:1 adducts in which the ratio of the unsaturated derivative XXXIX to the saturated derivative XL varies by a factor of 100 as the halide is varied from chloride to iodide. This is consistent with a classical intermediate in which rearrangement to the nortricyclene derivative is favored as the chain transfer efficiency of the addend is lowered. More important, dilution of any given halide brought about a decrease in the ratio of XXXIX to XL. Furthermore, it was found that when benzenesulfonyl iodide was the addend, the olefinic product was trapped before the rearrangement had proceeded to the extent of 17%.

The role of the chain transfer agent as a product determining entity was examined by several other workers.³⁸⁻⁴⁰ Trecker and Henry,³⁸ for example, observed that the chain transfer constant of those addends which give only the nortricyclene derivatives are consistently low while that of thiophenol, which gives 72% of the nortricyclene derivative and 28% of the unsaturated sulfide, is markedly higher. A competitive experiment in which norbornene and norbornadiene were allowed to compete for the trichloromethyl radical showed that the non-classical radical need not be considered as a significant product determining species. The results of Trecker and Henry demonstrated that norbornadiene is only two times more reactive than norbornene. Thus, the olefinic bonds in the former are only additive.

Recently, Claisse and Davies⁴² reported that the radical addition of *p*-thiocresol to hexachloronorbornadiene yields only the endo addition product XLI and the rearranged sulfide XLII. The authors make no attempt to rationalize these results.

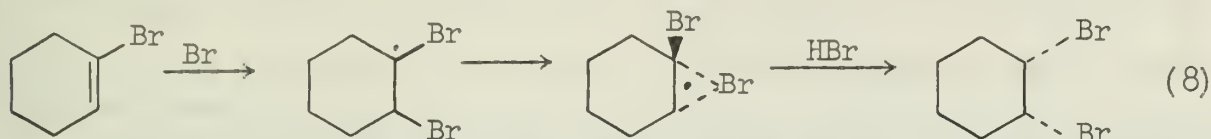


THE BRIDGED-HALOGEN RADICAL

Relatively little work has been done in this area of free radical chemistry. Unlike the non-classical free radical in the bicyclic systems, however, there seems to be some evidence that the bridged-halogen radical, particularly the bridged-bromine radical, may be a significant intermediate in some halogenation and hydrohalogenation reactions.

The very early work in this area was done by Goering and coworkers.⁴³⁻⁴⁵ Goering, Abell, and Aycok⁴³ first proposed the bridged-bromine radical when they found that the peroxide or light initiated addition of HBr to 1-bromocyclohexene

and 1-methylcyclohexene yielded the cis-1,2-substituted compounds exclusively. These workers argue that since trans-1,2-substituted cyclohexanes are more stable than the cis, the radical attack is not random but involves a stereoelectronic effect. In order to yield the cis dibromide the reaction path requires a trans stereochemical course. According to Walling⁴⁶ this suggestion has been generally discounted because



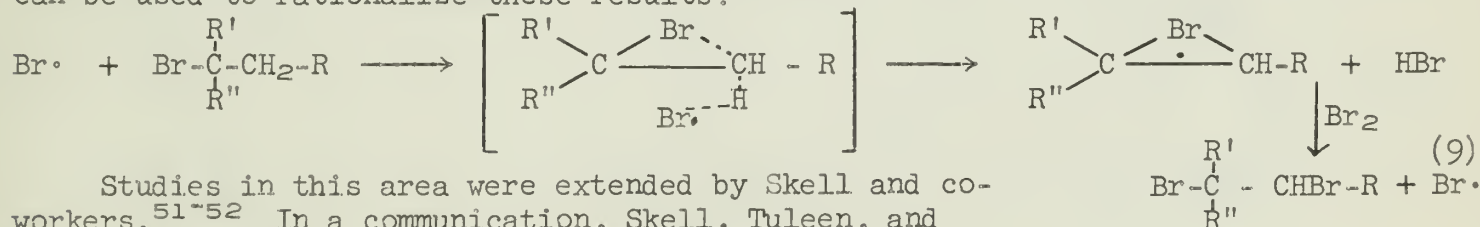
of comparably stereospecific addition of other radicals under conditions where no bridged radical can intervene.

Two other alternatives to the bridged-bromine radical have been proposed by Goering.^{44,47} Goering and Larsen⁴⁷ suggested a scheme wherein bromine addition is very closely followed by acquisition of hydrogen atom so that conformational changes in the initially formed bromoalkyl radical do not have time to take place. Goering and Sims⁴⁴ envision a possible scheme in which HBr initially complexes with the olefin through hydrogen; subsequent attack of bromine atom is accompanied by homolytic cleavage of the H-Br bond which produces another bromine atom.

Very little data bearing on these alternatives has been published. Although evidence available at present favors the bridged structure in some reactions of the bromine⁴⁸⁻⁵³ and iodine⁵⁴ radicals, its existence has been seriously questioned in these reactions.^{28-30,55-59} Abell and Piette⁴⁹ utilized e.s.r. to seek information pertaining to the structure of the radical intermediate in the light induced reactions of HBr with a series of olefins and acetylenes at 77°K. They obtained spectra which appeared to be consistent with a bridged-bromine radical or with a situation where two classical radicals are in rapid equilibrium. In the only other e.s.r. study reported, Mitchell, Greene, and Spinks⁶⁰ examined the gamma-ray initiated reaction of HBr with ethylene in the gas phase. These workers were not able to obtain any evidence for $\cdot\text{CH}_2\text{CH}_2\text{Br}$.

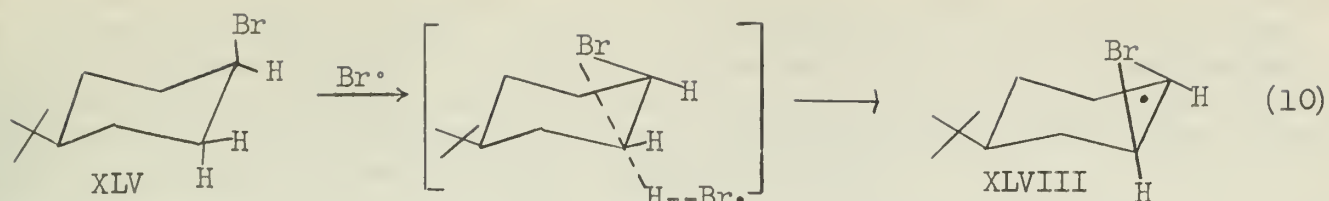
The interpretations of Abell and Piette are questioned by Symons⁵⁶ who claims that the radicals observed by the workers could well have been delocalized allylic radicals. The question remains unresolved to the present time.

In the photobromination of alkyl halides, Thaler⁵⁰ observed isomer distributions which appear inconsistent with predictions that can be made from existing theories⁶¹ for free radical halogenations. For example, the free radical photobromination of bromocyclohexane gave only trans-1,2-dibromocyclohexane. The photobromination of chlorocyclohexane, however, yielded six bromochlorocyclohexanes as anticipated on the basis of existing theories. Thaler suggested that a neighboring group effect leading to the formation of the bridged-bromine radical can be used to rationalize these results:



Studies in this area were extended by Skell and co-workers.⁵¹⁻⁵² In a communication, Skell, Tuleen, and Readio⁵¹ report that the radical chain bromination of (+)-1-bromo-2-methylbutane (XLIII) yields (-)-1,2-dibromo-2-methylbutane (XLIV) in high optical purity. Chlorination of XLIII, on the other hand, yielded inactive 1,2-dihalide. These workers suggest that this difference requires a mechanistic scheme analogous to (9) wherein bromine assists in the departure of the 3° hydrogen atom.

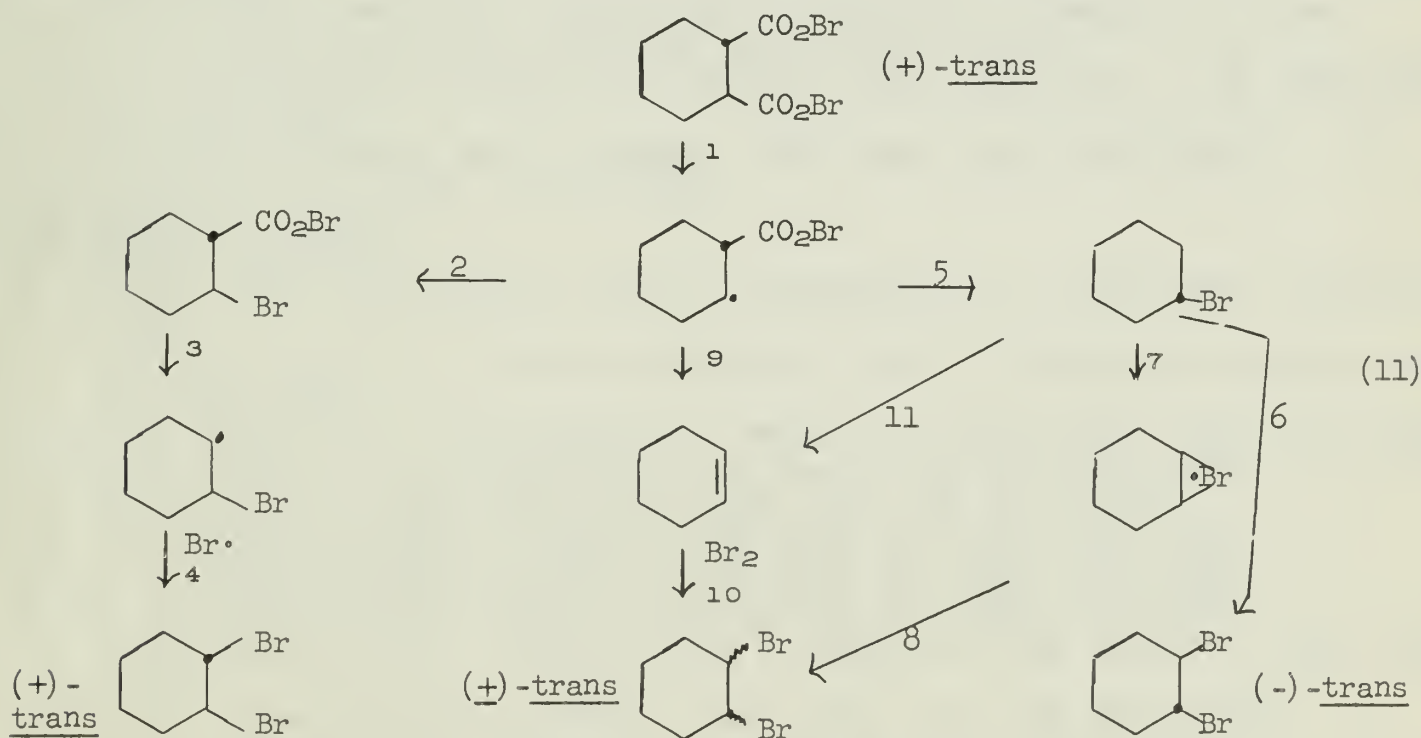
Skell and Readio⁵² present a strong case for a bridged radical by showing that the photobromination of cis-4-bromo-t-butylcyclohexane (XLV) yields more than 90% of trans-3-cis-4-dibromo-t-butylcyclohexane (XLVI) while the same reaction with trans-4-bromo-t-butylcyclohexane (XLVII) shows considerably less selectivity to the attack of bromine atoms. The axial bromine atom in XLV is able to assist in the hydrogen abstraction by bridging to give radical XLVIII which then opens in accordance with



the "diaxial rule."⁶² In XLVII the equatorial bromine atom is unable to undergo this sequence.

Evidence has been presented which sheds doubt upon the existence of the bridged-halogen radical. As a result of more extensive work, Goering and Sims⁴⁴ concluded that the free radical hydrobromination of 1-chloro- and 1-bromocyclohexene can be rationalized in terms of radical attack of the bromine atom on the cyclohexene from the axial direction followed by reaction of the intermediate with HBr at the axial position. This scheme would explain the trans addition and cis dihalide. LeBel and coworkers⁵⁸ found that the free radical addition of HBr to 2-chloro-2-norbornene yields a mixture of endo-cis-2-bromo-3-chloronorbornane and exo-2-bromo-endo-3-chloronorbornane in a ratio of 3:7. The intervention of the bridged radical would be expected to give, in addition to the endo-cis dihalide, at least some exo-cis dihalide. The investigations of Berson and coworkers²⁸⁻³⁰ concerning the cis-bromination in bicyclic olefins also seem to preclude the intervention of the bridged radical since no evidence was found that the trans-1,2-dibromide is formed by a free radical process. Benson and coworkers⁵⁹ use thermochemical and kinetic data in their arguments against Skell's⁵⁴ suggestion that the bridged iodine radical intervenes in the photoiodination of 2-butenes.

Recently, Applequist and Werner⁵⁷ showed that while the brominative decarboxylation of silver-(+)-trans-1,2-cyclohexanecarboxylate (XLIX) proceeds with a net inversion of configuration, the intervention of the bridged-bromine radical is not consistent with the data. The optical purity of product was not affected by a three-fold increase in initial bromine concentration. In addition, while specific rotations of products obtained under various conditions approached zero, they were always negative. Reaction series (11) shows the possible paths by which the pro-



duct can be formed. Since the optical activity varies, an inversion pathway and either a retention pathway or a pathway leading to a racemic product must be operating in competition. Reactions 1-4 are expected to yield the (+)-trans product. An increase in initial bromine concentration would be expected to favor 2 over 5. Since this is not the case, reactions 1-4 probably do not contribute significantly. The same is true of reaction 7. Failure of a three-fold increase

of bromine to change the optical activity of product suggests that the formation of the bridged-bromine radical does not occur and that reaction 7 is not the racemate-producing pathway. Applequist and Werner concluded that the pathways which best explain their results are reactions 1,5,6,9,10, and 11. They also suggested that some heterogeneous process not shown in the scheme causes racemization and adds to the very erratic optical activity.

SUMMARY

Experimental evidence gathered over the past decade convincingly shows that the non-classical radical analogous to the mesomeric carbonium ion in bicyclic systems need not be invoked as a rate or product determining species. Kinetic evidence failed to show sigma- or pi-assistance in the formation of radicals from exo-substituted bicyclic compounds. Product distribution studies failed to detect products that would require the intervention of the non-classical radical to explain their formation. No evidence of any kind as yet has been found that would lend support to such a species.

In the case of the bridged-halogen radical intermediate, however, no general conclusion can be reached. It appears that the formation of this intermediate may be highly dependent on the reaction and conditions used. It has been clearly shown that it cannot be invoked generally.

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THE NON-CLASSICAL FREE RADICAL

Reported by Z. M. Holubec

August 11, 1965

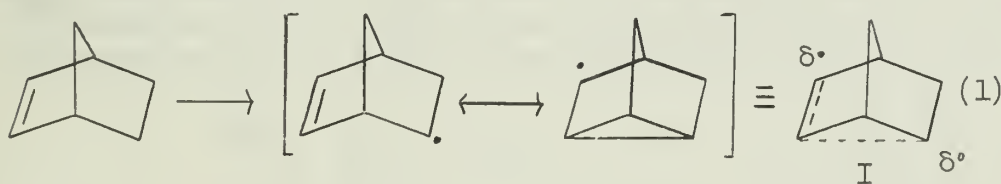
INTRODUCTION

As workers in the field of carbonium ion chemistry were demonstrating the wide applicability of the concept of the non-classical carbonium ion in explaining product distribution, stereochemistry, and rate enhancement toward solvolysis of certain molecules, investigators in the field of free radical chemistry began examining the analogous free radical systems for similar phenomena. Although the literature concerning the latter field is not as voluminous as that for carbonium ions, a great deal of useful information regarding the properties of free radicals has been obtained.

Several excellent reviews dealing with free radical rearrangement,¹⁻³ formation of carbon-carbon bonds⁴ and carbon-hetero bonds⁵ through radical processes were recently published. A comprehensive monograph⁶ covering the literature on solution free radical chemistry up to approximately 1956 is also available. This discussion will be limited primarily to the question of non-classical free radicals in bicyclic systems and its relationship to the observed rearrangements and the bridged halogen radical in halogenation and hydrohalogenation reactions.

THE NON-CLASSICAL FREE RADICAL IN BICYCLIC SYSTEMS

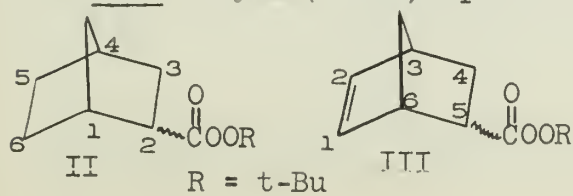
Carbonium ions in the rigid skeletal structures of bicyclic systems have attracted a great deal of attention. An excellent review concerning this subject has recently appeared.⁷ Of the large amount of evidence supporting the existence of the non-classical carbonium ion in these systems the most convincing is the tremendous rate enhancement observed in the solvolysis of exo-substituents and the demonstration that the rearranged products obtained can be rationalized on the basis of a single intermediate species, the mesomeric cation. Presumably, the former effect is due to sigma- or homoallylic pi-bond participation in the transition state. It is not unexpected that the same approach should be used by the workers in the free radical field in seeking evidence for or against the existence of a similar rate or product determining intermediate in bicyclic free radicals. Roberts and coworkers⁸ appear to be the first to have suggested the possibility of a non-classical radical in their work on the benzoyl peroxide initiated reaction of norbornene with N-bromosuccinimide in carbon tetrachloride. They found that 3-bromonortricyclene was produced in 27-40% yield. It was suggested that the orientation of orbitals in the rigid bridged-ring system favored interaction with the radical site:



Several other workers,⁹⁻¹⁴ studying free radical reactions of bicyclic derivatives in the early 1950's, failed to find re-

arranged products similar to those found in the analogous carbonium ions. Berson and coworkers,¹⁵ however, point out that in most of the reactions described earlier the yields of identifiable products are only moderate and that it is difficult to decide whether or not rearrangement is a prohibitive process.

Anchimeric assistance in the decomposition of 2-norbornyl- and 5-norbornenyl peroxyates and peroxides was investigated by Martin and DeJongh¹⁶ and by Hart and Chloupek,¹⁷ respectively. Martin and DeJongh compared the rates of homolytic cleavage of bonds exo and endo to the ethano bridge in the t-butyl peresters of exo- and endo-bicyclo(2.2.1)heptane-2-carboxylic acid (IIx and IIIn) and exo- and endo-



bicyclo(2.2.1)hept-5-ene-2-carboxylic acid (IIIx and IIIIn). As in the carbonium ion analogue,⁷ participation by the C1-C6 single bond or C1-C2 double bond should be reflected in the rate of decomposition and the activation parameters of the

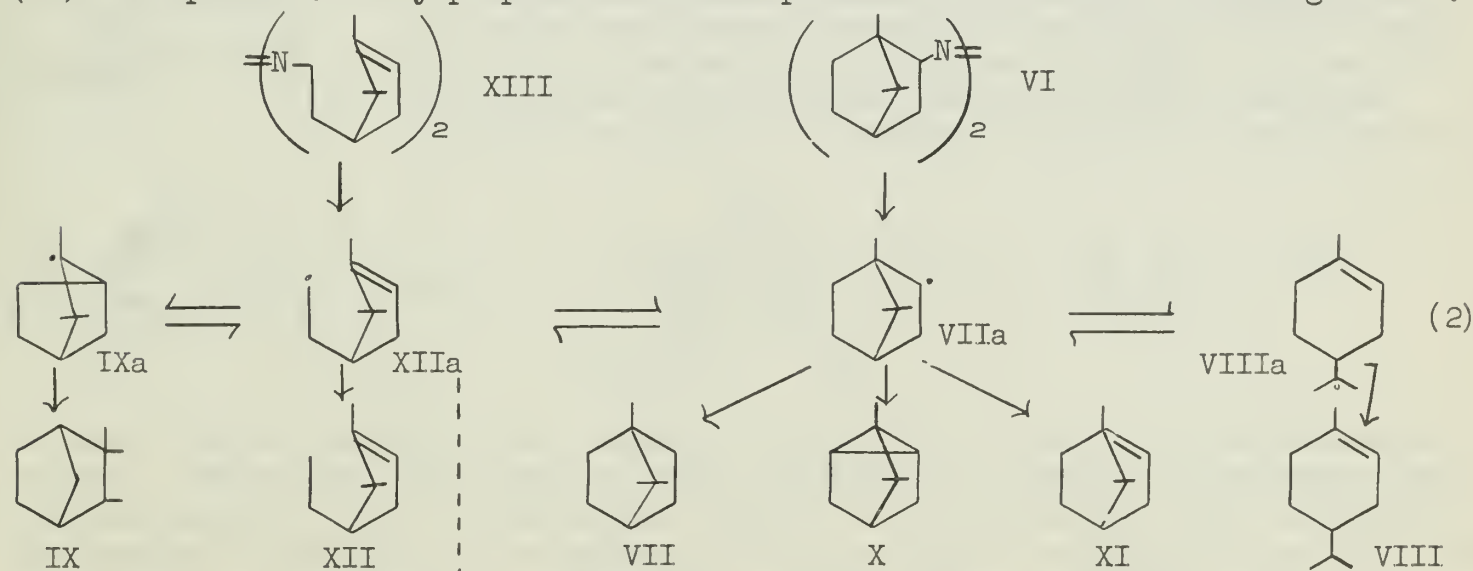
exo and endo pairs. If there is no sigma- or pi-bond participation then the rates and activation parameters should be the same in the decomposition of each pair. These predictions are based upon the investigations of Bartlett and his students.¹⁸⁻²¹ In the transition state of a concerted decomposition there is of necessity a restricted rotation around bond b because elimination of the alkyl and t-butoxy radicals must be trans. There is no such restriction in a stepwise elimination. The mechanism by which this decomposition occurs is characterized by the values of the activation parameters ΔH^* and ΔS^* . In a mechanism involving no rotational restrictions in the transition state, the values of ΔH^* were found to be greater than 35 kcal/mole and ΔS^* of greater than 13 e.u. A concerted mechanism, on the other hand, is characterized by values of ΔH^* of 30-35 kcal/mole and ΔS^* of 6-13 e.u.

The kinetic experiments of Martin and DeJongh in cumene demonstrated that the rates of decomposition of each of the two pairs were essentially identical. The calculated ΔH^* for IIx and IIIn were 31.4 and 31.1 kcal/mole while the ΔS^* was 7 and 6 e.u., respectively. For IIIx and IIIn the corresponding ΔH^* values were found to be 33.0 and 32.6 kcal/mole and the ΔS^* , 11 and 9 e.u., respectively. On the basis of these results, Martin and DeJongh concluded that decomposition proceeds through a concerted mechanism and that it is not energetically more favorable for an exo bond to undergo scission than it is for an endo bond. Therefore, neither sigma- nor pi-participation can be construed to be a significant driving force in these reactions.

Recently, Bartlett and McBride²² reinvestigated the decomposition of IIx and IIIn. Although conclusions regarding the sigma- and pi-participation were the same as those of Martin and DeJongh, they found that IIx decomposes at about three times the rate of IIIn. The activation parameters, however, still fall well within the range predicted by model compounds.

Similar conclusions were reached by Hart and Chloupek¹⁷ after investigating the kinetics of the decomposition of the diacyl peroxides from exo- and endo-norbornane-2-carboxylic acid (IVx and IVn) and exo- and endo-norbornene-5-carboxylic acids, (Vx and Vn). They found that although IVx decomposes at 7-10 times more rapidly than IVn, the peroxides Vx and Vn decompose at essentially identical rates. The observed acceleration of IVx over IVn was attributed to a steric factor.

Several workers^{15,23-30} studied the behavior of the 2-norbornyl and related radicals under a variety of conditions. Berson, Olsen, and Walia¹⁵ found that among the products isolated from the decomposition of 2-azocamphane, bornane (VII), 1-p-menthene (VIII), 2,3,3-trimethylnorbornane (IX), tricyclene (X), and bornene (XI) were present. They propose that these products arise in the following manner:



The radical XIIa was prepared independently by decomposition of XIII. Under the conditions used to decompose VI, azo compound XIII yielded a complex mixture of

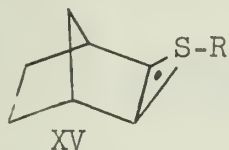
products in which VII and IX were present. Hence, it was concluded that VIIa is probably the immediate product of the decomposition of VI, and an equilibrium between VIIa and XIIIa must exist.

The question which immediately arises is what part, if any, a mesomeric free radical (XIV) plays in the observed rearrangement. Berson and coworkers concluded that no analogy can be drawn between this and the structurally similar carbonium ion process. The decomposition of VI and XIII occur at rates which are essentially the same as those of simple model compounds in which anchimeric assistance is absent. Furthermore, in the rearrangement of VI to IX, there is no stereospecificity or selectivity and both possible stereoisomers are produced. This observation makes it difficult to reconcile the observed products with XIV as the sole intermediate. In addition, ratios of the products obtained from the decomposition of VI and XIII clearly show that the amount of a given hydrocarbon is dependent on the azo compound decomposed. This suggests that a non-mesomeric radical is not rapidly converted to a common mesomeric product-forming intermediate. If a common intermediate formed from either azo compound, its fate would be independent of its precursor.

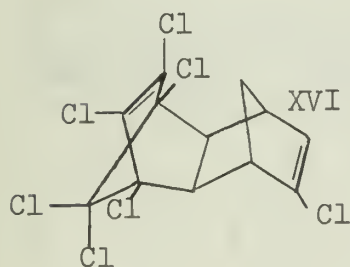


It may be significant that the ratio of any two products on a given side of the dotted line in the mechanistic scheme (2) is independent of the time and source of radicals while the ratio of any two products on opposite sides of the dotted line, while also independent of time, is not independent of the source of the radicals. For these ratios to be independent of starting material, a very rapid conversion of XIIIa to VIIa or a common intermediate would be anticipated. Therefore, it was concluded that at least the major portion of the observed rearrangement must be going through classical radicals.

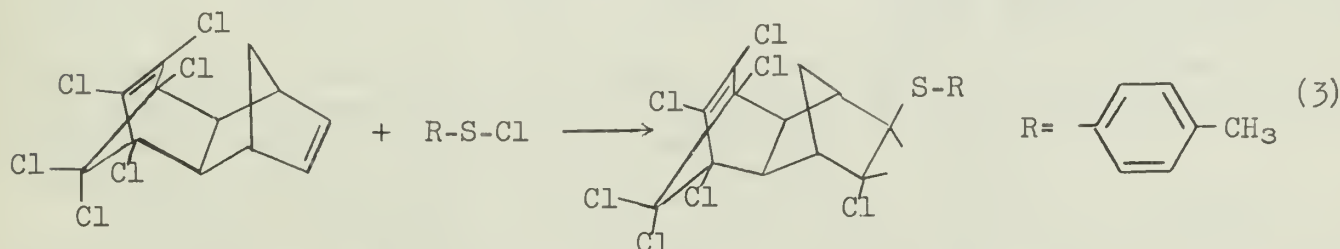
Research groups under the direction of Cristol and Berson sought to provide evidence for or against the non-classical free radical in the norbornyl system by radical additions to norbornenes. Cristol and Brindell²⁴ have shown that addition of *p*-thiocresol to norbornene yields only *exo*-norbornyl-*p*-tolylthioether in 85% yield. Thus, no rearrangement analogous to the Wagner-Meerwein occurred and an intermediate such as XIV need not be invoked in order to rationalize the data. Cristol and Arganbright²⁵ also demonstrated that a radical such as XV need not be



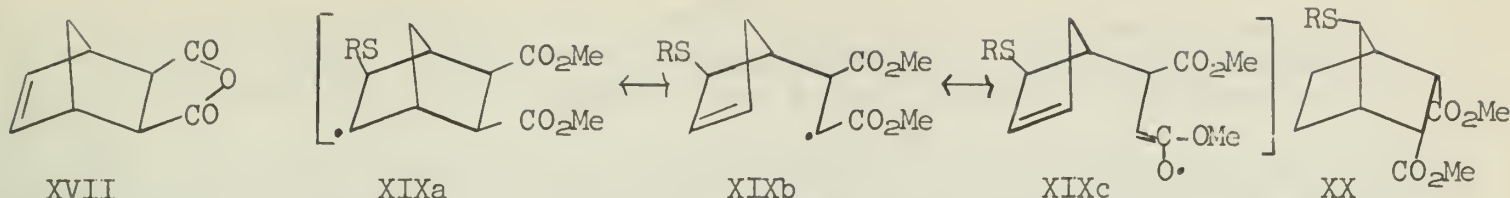
considered as a significant intermediate in the addition of mercaptans to bicyclic olefins. Addition of *p*-thiocresol to 6-chloroaldrin (XVI) afforded only one product which was identical with that obtained from the addition of *p*-toluenesulfonyl chloride to aldrin and shown to have *trans* stereochemistry relative to chlorine and the sulfide group.³¹ Thus, the free radical addition to XVI is *cis* and not consistent with a radical intermediate such as XV.



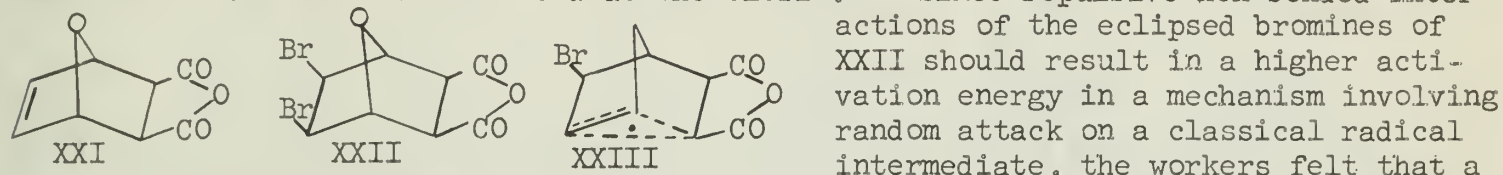
Berson and Jones³² added *p*-thiocresol to *exo-cis*-3,6-endomethylene- Δ^4 -tetrahydrophthalic anhydride (XVII) as well as to its corresponding dimethyl ester (XVIII). A quantitative analysis for rearranged products was then conducted using isotope dilution techniques. Under the conditions used



by these workers, the method was capable of detecting as little as 0.6% rearranged product. The authors postulate that XVII and XVIII are capable of sustaining a free electron because of the delocalization (XIXa-c) in the transition state leading to rearrangement. However, the experiment failed to produce any *endo* diester, XX, which would have been produced if rearrangement occurred. These workers concluded that delocalization shown by structures XIX does not play a significant role even under what is presumed to be the most favorable of conditions.

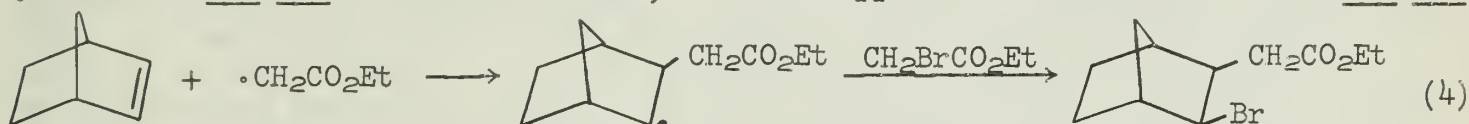


Berson and Swidler²⁸⁻²⁹ found that the bromination of exo-cis-3,6-endo-oxo- Δ^4 -tetrahydrophthalic anhydride (XXI) yields 36% of the cis dibromide XXII. Control experiments showed that XXII formed as a result of a free radical process. The same reaction occurs when XVII is used as the olefin.³⁰ Since repulsive non-bonded inter-



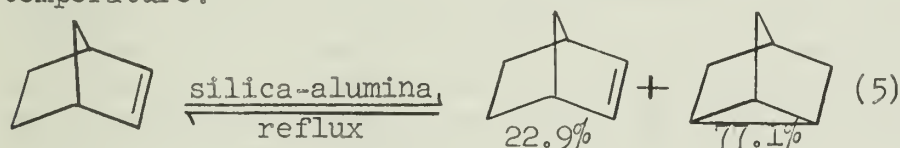
actions of the eclipsed bromines of XXII should result in a higher activation energy in a mechanism involving random attack on a classical radical intermediate, the workers felt that a

powerful stereoelectronic factor leading to XXII was operative. They proposed that the non-classical radical XXIII intervened as a product determining species. Walling,³³ however, notes that the stereochemistry is apparently the same as that observed by Weinstock³⁴ who found that addition of ethylbromoacetate to norbornene yields the exo-cis derivative. Thus, it would appear that formation of the exo-cis



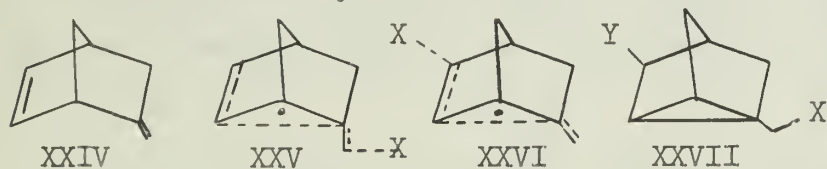
derivative is a manifestation of a steric rather than a stereoelectronic effect.

Because of the favorable position of the homoallylic double bond, the 5-norbornenyl free radical has attracted much attention from workers searching for evidence for non-classical free radicals.^{16-17,26-27,35-40} In almost all cases studied the 5-norbornenyl radical gives predominantly the nortricyclene rearranged product. This result is hardly surprising in view of the thermodynamically favored product when norbornene is equilibrated in presence of silica-alumina at reflux temperature.⁴¹



One of the more interesting systems studied is 5-methylenenorbornene (XXIV). Attack at either olefinic bond may result in homoconjugative

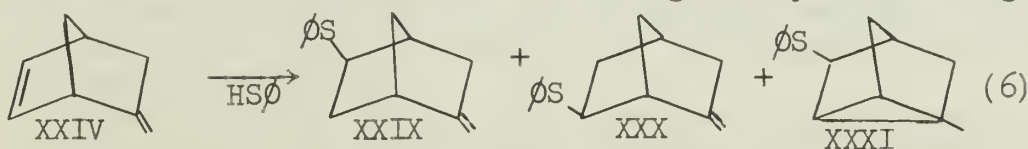
addition through delocalized species XXV and XXVI. Huyser and Echegaray²⁷ found that the exocyclic double bond is more reactive toward free radical addition of carbon tetrachloride, chloroform, and bromotrichloromethane and that the predominant product is the nortricyclene derivative XXVII. The conclusion regarding the relative



reactivity of the two olefinic bonds was confirmed by a competition experiment between 2-methylenenorbornane (XXVIII) and norbornene. It was found that the exocyclic double bond was about four times as

reactive as the endocyclic double bond. These workers also published evidence that the delocalized species XXV was not involved in the homoconjugative addition by a competitive reaction involving XXIV and XXVIII. It was observed that the total reactivity of XXIV is only 28% greater than that of XXVIII.

Recently, Cristol and coworkers²⁶ studied the addition of thiophenol to XXIV and found that the endocyclic double bond is more reactive toward this reagent. The nature of the intermediate was investigated by determining the effect of mercaptan



concentration on the ratio of XXIX to XXXI. If the radical intermediate is non-classical, then there

should be no effect on the ratio. If, on the other hand, two classical radicals are

involved, dilution of mercaptan will result in a slower chain transfer and favor isomerization to XXXI. Dilution of mercaptan produced a significant decrease in the ratio. Therefore, it was concluded that a non-classical radical was not involved.

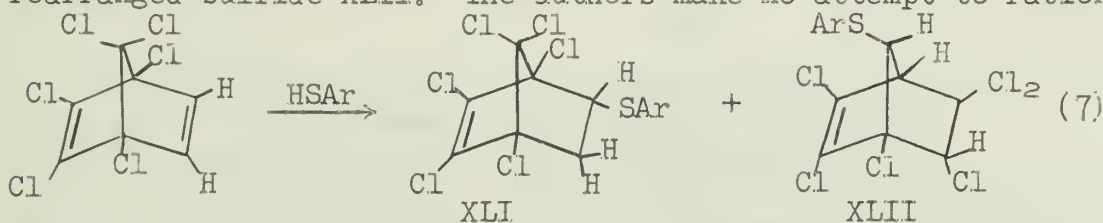
Wilt and Levin³⁵ generated radicals XXXII-XXXV via the decarbonylation of the corresponding aldehydes. They found that only XXXIII rearranged and then only to nortricyclene. In spite of low yields of hydrocarbons (typically less than 10%), they concluded that the non-classical radical XXVI or the kinetically equivalent



rapid equilibration of classical radicals XXXVII and XXXVIII were intermediates. This conclusion was drawn on the basis of the observation that dilution of substrate had no significant effect on the ratio of norbornene to nortricyclene. Earlier, Cristol and Brindell³⁶ had shown that in the addition of *p*-thiocresol to norbornadiene the ratio of the norbornene to the nortricyclene derivative decreased as the concentration of mercaptan was lowered. They concluded that neither the non-classical radical nor the equilibration can be involved in the product determining step. In subsequent work, Cristol and Davies³⁷ showed that this conclusion is valid. Addition of various halides to norbornadiene gives 1:1 adducts in which the ratio of the unsaturated derivative XXXIX to the saturated derivative XL varies by a factor of 100 as the halide is varied from chloride to iodide. This is consistent with a classical intermediate in which rearrangement to the nortricyclene derivative is favored as the chain transfer efficiency of the addend is lowered. More important, dilution of any given halide brought about a decrease in the ratio of XXXIX to XL. Furthermore, it was found that when benzenesulfonyl iodide was the addend, the olefinic product was trapped before the rearrangement had proceeded to the extent of 17%.

The role of the chain transfer agent as a product determining entity was examined by several other workers.³⁸⁻⁴⁰ Trecker and Henry,³⁸ for example, observed that the chain transfer constant of those addends which give only the nortricyclene derivatives are consistently low while that of thiophenol, which gives 72% of the nortricyclene derivative and 28% of the unsaturated sulfide, is markedly higher. A competitive experiment in which norbornene and norbornadiene were allowed to compete for the trichloromethyl radical showed that the non-classical radical need not be considered as a significant product determining species. The results of Trecker and Henry demonstrated that norbornadiene is only two times more reactive than norbornene. Thus, the olefinic bonds in the former are only additive.

Recently, Claisse and Davies⁴² reported that the radical addition of *p*-thiocresol to hexachloronorbornadiene yields only the *endo* addition product XLI and the rearranged sulfide XLII. The authors make no attempt to rationalize these results.

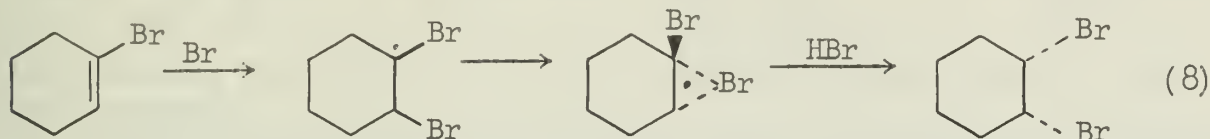


THE BRIDGED-HALOGEN RADICAL

Relatively little work has been done in this area of free radical chemistry. Unlike the non-classical free radical in the bicyclic systems, however, there seems to be some evidence that the bridged-halogen radical, particularly the bridged-bromine radical, may be a significant intermediate in some halogenation and hydrohalogenation reactions.

The very early work in this area was done by Goering and coworkers.⁴³⁻⁴⁵ Goering, Abell, and Aycok⁴³ first proposed the bridged-bromine radical when they found that the peroxide or light initiated addition of HBr to 1-bromocyclohexene

and 1-methylcyclohexene yielded the cis-1,2-substituted compounds exclusively. These workers argue that since trans-1,2-substituted cyclohexanes are more stable than the cis, the radical attack is not random but involves a stereoelectronic effect. In order to yield the cis dibromide the reaction path requires a trans stereochemical course. According to Walling⁴⁶ this suggestion has been generally discounted because



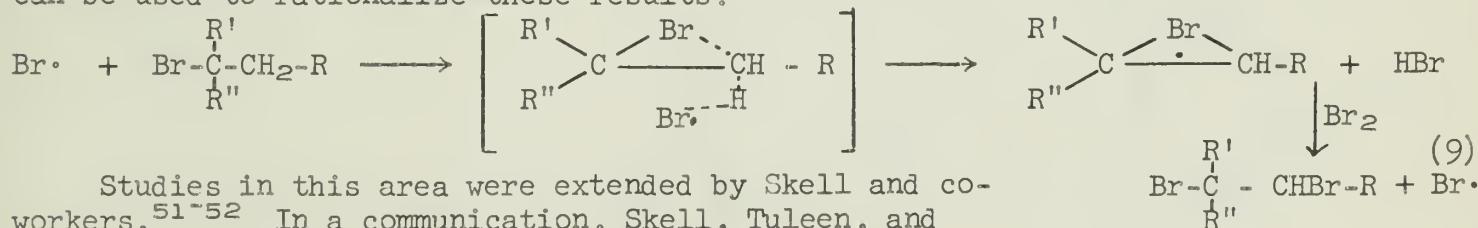
of comparably stereospecific addition of other radicals under conditions where no bridged radical can intervene.

Two other alternatives to the bridged-bromine radical have been proposed by Goering.^{44,47} Goering and Larsen⁴⁷ suggested a scheme wherein bromine addition is very closely followed by acquisition of hydrogen atom so that conformational changes in the initially formed bromoalkyl radical do not have time to take place. Goering and Sims⁴⁴ envision a possible scheme in which HBr initially complexes with the olefin through hydrogen; subsequent attack of bromine atom is accompanied by homolytic cleavage of the H-Br bond which produces another bromine atom.

Very little data bearing on these alternatives has been published. Although evidence available at present favors the bridged structure in some reactions of the bromine⁴⁸⁻⁵³ and iodine⁵⁴ radicals, its existence has been seriously questioned in these reactions.^{28-30,55-59} Abell and Piette⁴⁹ utilized e.s.r. to seek information pertaining to the structure of the radical intermediate in the light induced reactions of HBr with a series of olefins and acetylenes at 77°K. They obtained spectra which appeared to be consistent with a bridged-bromine radical or with a situation where two classical radicals are in rapid equilibrium. In the only other e.s.r. study reported, Mitchell, Greene, and Spinks⁶⁰ examined the gamma-ray initiated reaction of HBr with ethylene in the gas phase. These workers were not able to obtain any evidence for $\cdot\text{CH}_2\text{CH}_2\text{Br}$.

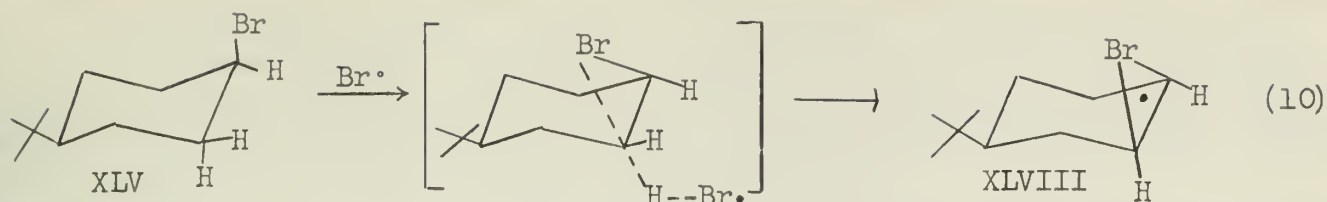
The interpretations of Abell and Piette are questioned by Symons⁵⁶ who claims that the radicals observed by the workers could well have been delocalized allylic radicals. The question remains unresolved to the present time.

In the photobromination of alkyl halides, Thaler⁵⁰ observed isomer distributions which appear inconsistent with predictions that can be made from existing theories⁶¹ for free radical halogenations. For example, the free radical photobromination of bromocyclohexane gave only trans-1,2-dibromocyclohexane. The photobromination of chlorocyclohexane, however, yielded six bromochlorocyclohexanes as anticipated on the basis of existing theories. Thaler suggested that a neighboring group effect leading to the formation of the bridged-bromine radical can be used to rationalize these results:



Studies in this area were extended by Skell and co-workers.⁵¹⁻⁵² In a communication, Skell, Tuleen, and Readio⁵¹ report that the radical chain bromination of (+)-1-bromo-2-methylbutane (XLIII) yields (-)-1,2-dibromo-2-methylbutane (XLIV) in high optical purity. Chlorination of XLIII, on the other hand, yielded inactive 1,2-dihalide. These workers suggest that this difference requires a mechanistic scheme analogous to (9) wherein bromine assists in the departure of the 3° hydrogen atom.

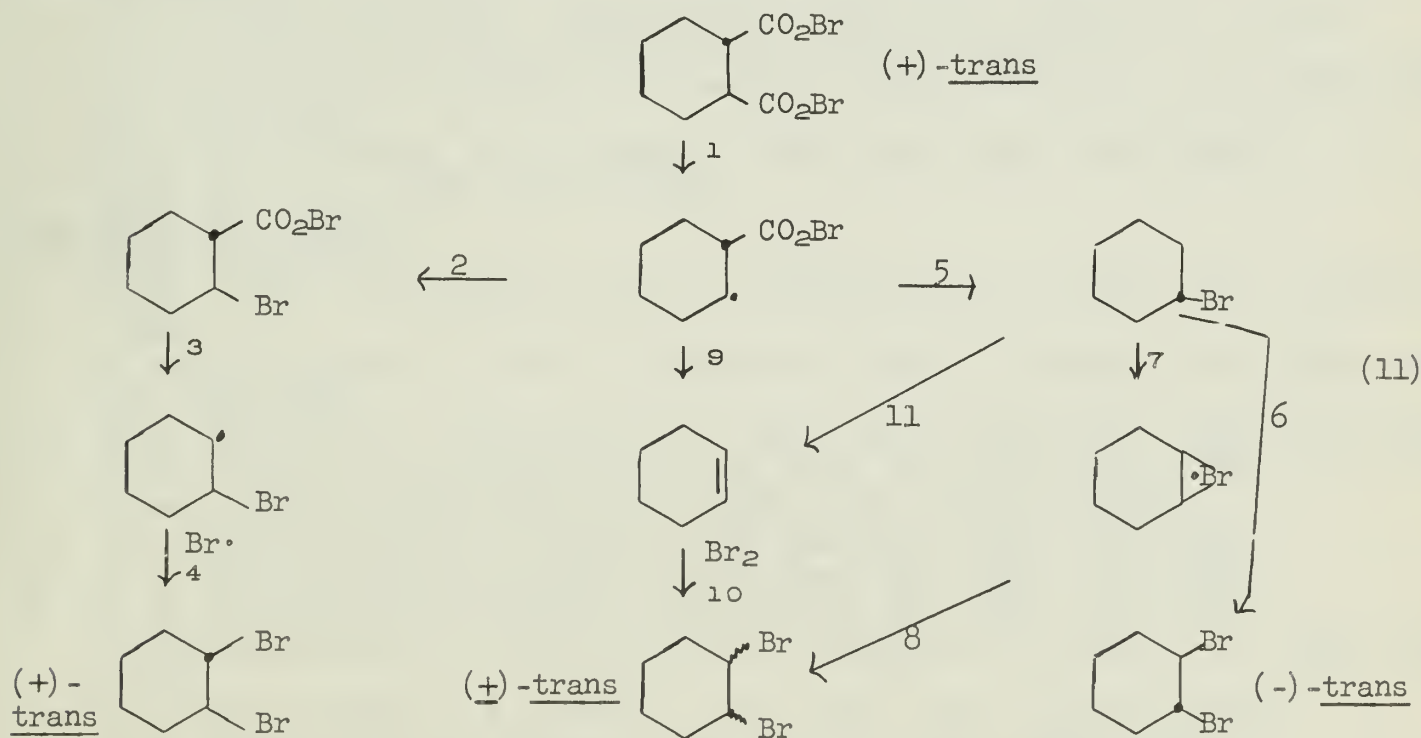
Skell and Readio⁵² present a strong case for a bridged radical by showing that the photobromination of cis-4-bromo-t-butylcyclohexane (XLV) yields more than 90% of trans-3-cis-4-dibromo-t-butylcyclohexane (XLVI) while the same reaction with trans-4-bromo-t-butylcyclohexane (XLVII) shows considerably less selectivity to the attack of bromine atoms. The axial bromine atom in XLV is able to assist in the hydrogen abstraction by bridging to give radical XLVIII which then opens in accordance with



the "diaxial rule."⁶² In XLVII the equatorial bromine atom is unable to undergo this sequence.

Evidence has been presented which sheds doubt upon the existence of the bridged-halogen radical. As a result of more extensive work, Goering and Sims⁴⁴ concluded that the free radical hydrobromination of 1-chloro- and 1-bromocyclohexene can be rationalized in terms of radical attack of the bromine atom on the cyclohexene from the axial direction followed by reaction of the intermediate with HBr at the axial position. This scheme would explain the trans addition and cis dihalide. LeBel and coworkers⁵⁸ found that the free radical addition of HBr to 2-chloro-2-norbornene yields a mixture of endo-cis-2-bromo-3-chloronorbornane and exo-2-bromo-endo-3-chloronorbornane in a ratio of 3:7. The intervention of the bridged radical would be expected to give, in addition to the endo-cis dihalide, at least some exo-cis dihalide. The investigations of Berson and coworkers²⁸⁻³⁰ concerning the cis-bromination in bicyclic olefins also seem to preclude the intervention of the bridged radical since no evidence was found that the trans-1,2-dibromide is formed by a free radical process. Benson and coworkers⁵⁹ use thermochemical and kinetic data in their arguments against Skell's⁵⁴ suggestion that the bridged iodine radical intervenes in the photoiodination of 2-butenes.

Recently, Applequist and Werner⁵⁷ showed that while the brominative decarboxylation of silver-(+)-trans-1,2-cyclohexanecarboxylate (XLIX) proceeds with a net inversion of configuration, the intervention of the bridged-bromine radical is not consistent with the data. The optical purity of product was not affected by a three-fold increase in initial bromine concentration. In addition, while specific rotations of products obtained under various conditions approached zero, they were always negative. Reaction series (11) shows the possible paths by which the pro-



duct can be formed. Since the optical activity varies, an inversion pathway and either a retention pathway or a pathway leading to a racemic product must be operating in competition. Reactions 1-4 are expected to yield the (+)-trans product. An increase in initial bromine concentration would be expected to favor 2 over 5. Since this is not the case, reactions 1-4 probably do not contribute significantly. The same is true of reaction 7. Failure of a three-fold increase

of bromine to change the optical activity of product suggests that the formation of the bridged-bromine radical does not occur and that reaction 7 is not the racemate-producing pathway. Applequist and Werner concluded that the pathways which best explain their results are reactions 1,5,6,9,10, and 11. They also suggested that some heterogeneous process not shown in the scheme causes racemization and adds to the very erratic optical activity.

SUMMARY

Experimental evidence gathered over the past decade convincingly shows that the non-classical radical analogous to the mesomeric carbonium ion in bicyclic systems need not be invoked as a rate or product determining species. Kinetic evidence failed to show sigma- or pi-assistance in the formation of radicals from exo-substituted bicyclic compounds. Product distribution studies failed to detect products that would require the intervention of the non-classical radical to explain their formation. No evidence of any kind as yet has been found that would lend support to such a species.

In the case of the bridged-halogen radical intermediate, however, no general conclusion can be reached. It appears that the formation of this intermediate may be highly dependent on the reaction and conditions used. It has been clearly shown that it cannot be invoked generally.

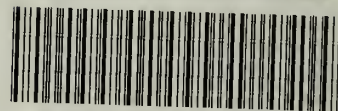
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